

A Clinical Survey of Fifty Cases of  
Exophthalmic Goitre, with Special Reference to  
the Pathology, Symptomatology, and Treatment of  
the Condition.

by

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Appendix - Synopsis of Twenty-Five Cases.

## I. Introduction

Exophthalmic goitre may be defined as a condition due to perverted or hyperactive state of the thyroid gland, and increased activity of the vegetative nervous system. It is characterised clinically by tachycardia and palpitation, goitre, exophthalmos, tremor, loss of weight and general nervous irritability. In addition there is a tendency for the condition to assume a crisis state - a phase of heightened intoxication, comparable to delirium tremens in chronic alcoholic poisoning - in which the nervous phenomena increase in severity, the patient thrashes about in bed, and should the crisis not be checked, goes on to vomiting, delirium, coma and death. Of these numerous phenomena the four cardinal signs are tachycardia, tremors, goitre and exophthalmos.

The disease, first described by Parry (1786) is also associated with the names of Flajani (1802), Graves (1835) and Basedow (1840), all of whom pointed out its chief symptoms. In the opinion of Osler, should the disease be given the name of any one physician, that name should be Parry, in whose posthumous/

posthumous writing is a description of eight cases with the main symptoms correctly described. While the Italians put forward the claims of Flajani, on the authority of Moebius, his effort was very imperfect, being a description of two cases of goitre with cardiac palpitation. Graves to whom the disease now owes its name, described three cases but believed that the pulsating tumour of the thyroid was due to the augmented action of the heart: while Basedow, who described four cases, thought both symptoms were secondary to a blood dyscrasia. The thyroid was not considered the primary affection until Moebius so insisted in 1887.

The symptoms cannot wholly be reduced to physiological terms, i.e. an excessive secretion of thyroxine cannot explain all the symptoms. The primary manifestations of excessive thyroid secretion are those which must accompany increased metabolism.

1. Tachycardia and palpitation indicative of increased output of blood by the heart.
2. Perspiration and warm skin indicative of increased heat elimination.
3. Good appetite associated with loss of weight indicative of increased food consumption, in most cases insufficient to maintain the body weight.
4. General nervous irritability indicative of fatigue.

But/



But the exophthalmos, the nervous unrest, the tremors, and the tendency to crises, are not explained by an increase of thyroid secretion; it is therefore suggested that these signs may be caused by perverted secretion. *Who suffers*

Some alienists, on the other hand, take a totally different view of the disease; they consider exophthalmic goitre is primarily a psychopathological condition, and classify it as an anxiety neurosis with protrusion of the eyeballs and enlargement of the thyroid as additional symptoms.

These and other modern ideas on the condition are discussed more fully in the next chapter.

My first acquaintance with exophthalmic goitre took place soon after entrance into hospital as a student of clinical medicine. The approach of the clinic caused one patient, a woman with wide staring eyes and an expression of intense fear, to tremble to such a degree that the very bed shook, visibly and audibly. I was much impressed.

Opportunity for an insight into the condition was afforded me while acting as house physician in Edinburgh Royal Infirmary - in a period of nine months I was privileged to attend thirty-three cases of the disease. Later while acting as house surgeon/

surgeon in Sunderland Royal Infirmary I was permitted through the kindness of the honorary physicians to treat the cases of exophthalmic goitre which came into the medical wards. In the course of twelve months seven cases passed through my hands. Lastly in general practice I have met with five cases in Haddington, East Lothian, and other five cases in Nelson, Lancashire. This makes in all a total of fifty cases.

In this thesis it is my intention to give a short account of the disease, chiefly in its clinical aspects, based on a series of fifty cases personally observed, and to illustrate the effect of iodine treatment in certain of them. In the appendix will be found a resume of twenty-five of the cases.

II - ETIOLOGY.

## II. Etiology.

We are quite ignorant of the cause of exophthalmic goitre, but certain factors appear to be present in a sufficient percentage of cases for us to assume that they have some relationship to the disease.

The part played by the thyroid gland is even yet not understood. While some believe that the disease has its origin in the gland itself, the balance of opinion now is that the condition is due to a stimulus from without acting on the gland. What this stimulus is has given rise to many conjectures. Is it some bacterial toxin acting directly on the gland, and goading it on to fresh activity which reacts on the metabolism of the whole body; or is it a call for help from the tissues to maintain the metabolism at an impossibly high level due to the influence of an unknown agency; or is the thyroid disturbance due to a primary lesion of the nervous system? We do not know.

The stimulus to destruction must be enormous. It may be some subconscious sex disturbance, possibly some psychic trauma, possibly some focal sepsis, possibly some lack of iodine. Worries, mental/



mental strain and shock are common in the histories of the cases; they apparently have a definite role. Infections, especially common in the teeth and tonsils are important, not only because of the exacerbations and relapses which they cause, but also because of the high level of intoxication which they maintain. Adolescence, and also pregnancy, the puerperium, and the menopause, appear to be danger epochs, associated with a heightened degree of intoxication.

Little is really known, however, farther than McCarrison's classification of factors causing hyperthyroidism - nutritional, psychic and toxic. Of these a combination of the last two appears to be the most important.

The etiology is discussed under two heads:

(1) Predisposing Factors.

(2) Theories on Exophthalmic Goitre - its Pathogenesis.

(1) Predisposing Factors.

Incidence: Sex: Familial Predisposition:

Marriage: A Human Disease: Geographical Distribution:

Nervous Shock and Strain: Infection:

Diet: Secondary Growths: Exposure of Ovaries to Radium.

(2) /

(2) Pathogenesis.

Hyperthyroidism: Hyperthyroidism and Dysthyroidism: Hypothyroidism and Dysthyroidism: A Neurosis: The Sympathetic Nervous System: A Pluriglandular Disorder: A Neuroglandular Disorder: An Infection: Iodine in the Causation: A Diathesis.

Incidence of the Disease.

Age.

The disease is rare at the extremes of life; the maximum incidence would seem to be between 16 and 40. This is the period of greatest activity of the endocrine glands and in women corresponds to the period of their functional activity.

Statistics as to age incidence are hard to obtain; it does not seem possible to make a true inference from mortality tables as many cases recover.

Of Buschan's <sup>(2)</sup> collection of 495 cases, 15 were under 10 years of age, 352 between 16 and 40, 163 between 20 and 30, 69 between 40 and 50 and 31 over 50. Blackford <sup>(3)</sup> gives the following figures from the Mason Blackford-Dowling Clinic - Of 2645 cases coming to operation, 7 were under 10 years of age, 263 between 10 and 19, 823 between 20 and 29, 814 between 29 and 39, 551 between 40 and 49, 168 between 50 and 59, and 16 over 60.

While the condition is rare before puberty - of Sattler's <sup>(4)</sup> collection of 3477 cases, only 184 were under 16 years of age. Dreschfield, however, reported one case at the age of 3, and Divil another at the age of  $2\frac{1}{2}$ .

Plummer/

*Wishers as  
evidence regarding  
age at onset.*

(5)  
Plummer believes that 60% of cases occur before 40 years of age.

(6)  
Campbell states that true exophthalmic goitre is rare before puberty; is increasingly commoner from 14-24, still common from 25-34, relatively uncommon from 35-44, and much rarer after this age.

In the writer's series the following was the age distribution at the time of coming for treatment. Between 16-20, 4 cases; from 21-30, 15 cases; from 31-40, 14 cases; 41-50, 13 cases; above 50, 4 cases; the oldest being 55 years of age.

*(also as early as  
to age at onset)*

A more prevalent disease.

Exophthalmic goitre is becoming more common in England and Wales and also in Scotland. This statement is abundantly proved by the Registrar-  
(7)  
General's statistics of the last 16 years.

		1911	1912	1913	1914	1915	1916
Total Deaths	Male	40	35	42	38	32	47
	Female	371	385	368	434	400	399
	Total	411	420	410	472	432	446
Crude Annual Death Rate per million Living person	Rate						
	Male	2	2	2	2	2	3
	Female	20	20	19	23	21	20
	person	11	12	11	13	12	13

1917/

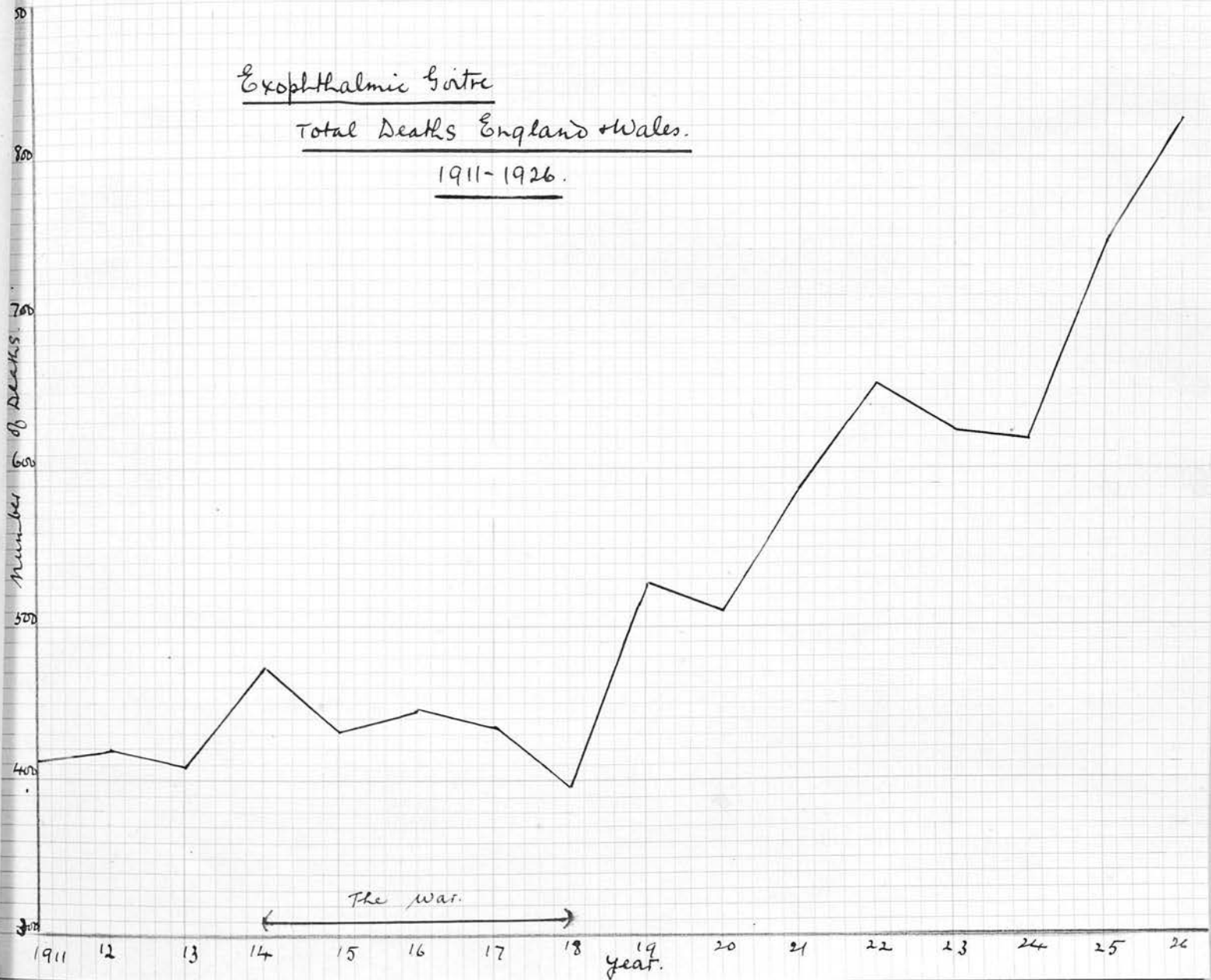


		1917	1918	1919	1920	1921	1922	1923	1924	1925	1926
1 hs	Male	40	46	56	46	54	63	56	46	64	84
	Female	395	351	473	464	533	591	569	574	680	743
	Total	435	397	529	510	587	654	625	620	744	827
le ual ch p. lion ing.	Male	3	3	4	3	3	3	3	2	3	4
	Female	20	18	24	24	27	30	28	28	34	36
	Person	13	12	15	14	15	17	16	16	19	21

*The person of the  
increase corresponds  
with the new  
myical  
insight*

These figures are also shown graphically.

Graph I /

Graph 1.Exophthalmic GoitreTotal Deaths England + Wales.1911-1926.

Age at Death.

During the three years 1924-26, the number of deaths returned in England and Wales from exophthalmic goitre was 2191, and the age distribution was as follows:-

	0-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75 -	80
M.	-	1	8	11	10	13	13	25	32	25	19	14	16	2	3	-
F.	1	9	69	121	101	141	198	238	290	304	203	152	110	40	13	7
Total	1	10	77	132	111	154	211	263	323	329	222	166	126	42	16	7
Sex Ratio	-	$\frac{1}{9}$	$\frac{1}{85}$	$\frac{1}{11}$	$\frac{1}{10}$	$\frac{1}{11}$	$\frac{1}{15}$	$\frac{1}{95}$	$\frac{1}{9}$	$\frac{1}{12}$	$\frac{1}{10}$	$\frac{1}{11}$	$\frac{1}{8}$	$\frac{1}{20}$	$\frac{1}{4}$	-

It will be seen from these figures and from the accompanying graph, that the number of deaths in each five year age period increases steadily up to 45-50, with the maximum number of deaths at 50-55, i.e. the maximum death rate is 45-55.

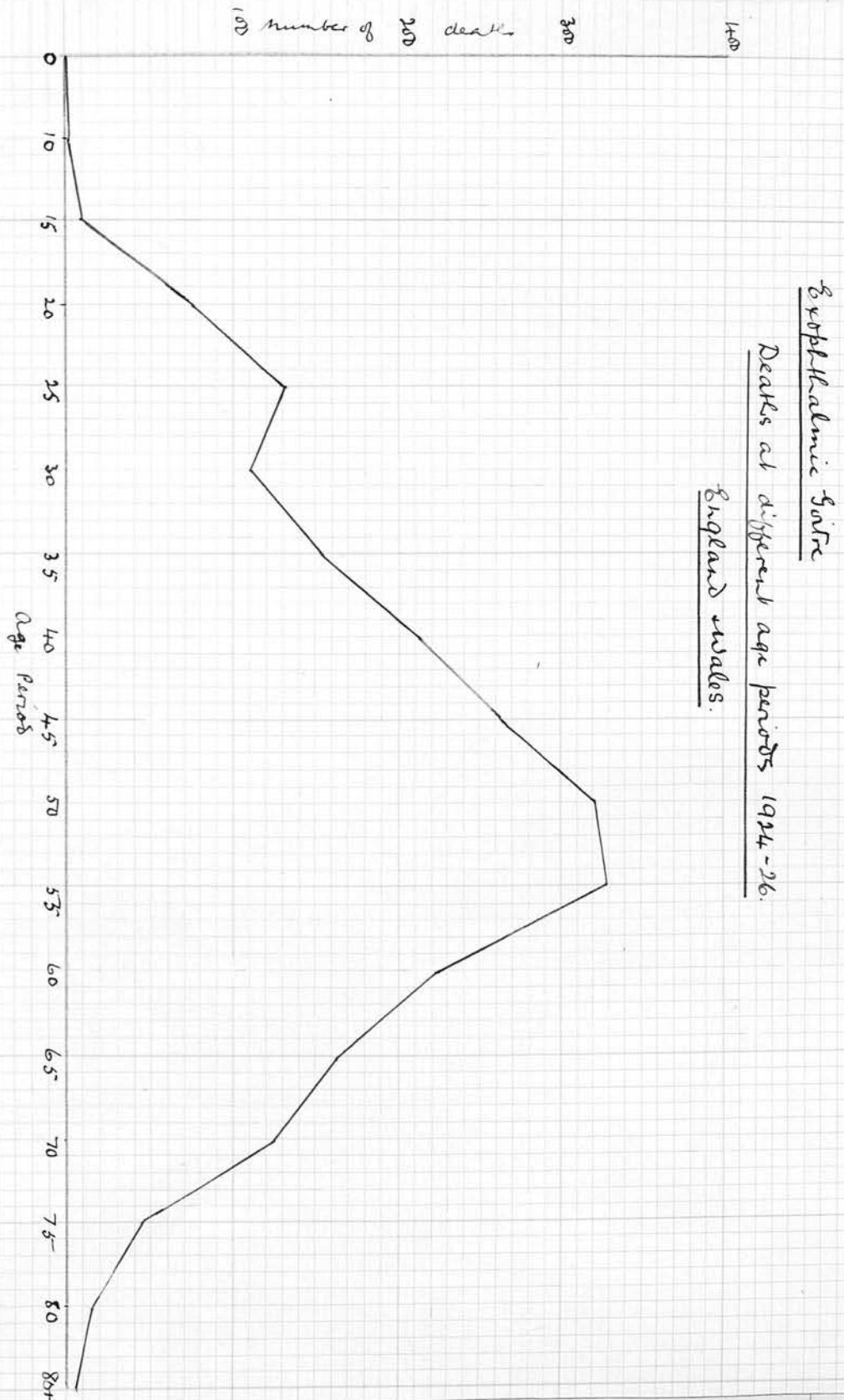
*possibly true but not "i.e."*

Two other series of three years have been studied and a similar age grouping was found.

It is also noteworthy that more than double the number of persons died from the disease over 65 than under 20 (191: 88 ).

A lesser point is that the sex ratio in all these age periods remained about the same throughout.

Graph 2 /

Graph 2.



The Scottish figures, while not so large, show very similar results, not only in the increase, but also in the age of maximum death rate and in the sex ratio.

Death Rate.

*Deaths but not death rate*

Year	Male	Fem.	Total	10-	15-	25-	35-	45-	55-	65-	75+
1915			65	-	7	10	15	19	8	4	2
1916			59	1	7	12	9	12	10	5	3
1920	9	41	50	-	5	6	18	14	5	2	-
1921	5	71	76	-	5	6	20	18	17	5	5
1922	6	70	76	-	8	6	26	17	13	5	1
1923	3	56	59	-	4	7	16	16	10	4	2
1924	5	70	75	1	8	15	14	17	13	7	-
1925	4	66	70	-	6	11	10	29	10	4	-
1926	11	75	86	-	11	17	21	21	13	3	-
	43	449	616	2	61	90	149	163	99	39	13

The condition is found in poor and rich alike. No class is immune from the condition. Statistics on such a point are obviously very imperfect, but the following show the place of death in England and Wales for 1918.

	<u>Male</u>	<u>Female</u>
Poor Law	-	9
Lunatic Asylums	2	14
Hospitals and Nursing Homes	6	45
Elsewhere	38	289

Sex.

The sex ratio is variously quoted as from 20:1 to 5:1. While it is probable that the sex ratio does vary in different countries, it is still more probable that since the disease is common in woman and relatively uncommon in man, the cases in the latter sex are looked upon as more noteworthy and are recorded.

In Sattler's collection the ratio was 5.4:1, and Buschan found that out of 980 cases, 805 were in women and 175 in men, a ratio of 9:2. Charcot reported that the disease was only slightly less common in men than in women, while Osler states that the ratio in England and America is definitely (8) much higher, being probably about 20:1. Letheby Tidy states that there are at least 10 female cases to 1 male case, and Price (9) about 6 females to 1 male. (10) Schafer gives the low figure of 4.6 to 1, and Plummer approaches this figure in reporting a group of 1036 patients treated at the Mayo clinic, of whom 822 were females and 182 males.

Between 1911-1926 there were 8519 deaths from the disease in England and Wales according to the Registrar General's reports; of these 789 were in men and 7730 in women, being a sex ratio of 10:1 (9.9) .

Other/

Other figures from the Registrar General's reports suggest a sex ratio of about 10:1, e.g. in the four years 1911-14, the number of deaths in England and Wales was 1558 for women and 155 for men and the distribution in the three years 1924-26 was 194 male deaths and 1997 female deaths. In Scotland for 1920-26 there were 43 male deaths and 449 female deaths, also a ratio of 10:1.

In the 50 cases observed by the writer 8 were in men and 42 in women, being a ratio of about 5:1. But these figures need qualification - they cannot be considered representative because of the type of case seen in Sunderland - excluding the Sunderland group there were three male cases and forty female cases.

*Not available.*

In this series the Sunderland group stand alone. Whereas the majority of cases seen elsewhere occurred in women in the earlier half of life, with vascular symptoms, the most prominent, this was not so in Sunderland. Of the 7 cases seen, 5 occurred in men, and in all but one there was a history of insidious onset, prolonged course, signs of marked degeneration of the cardiovascular system. The two female cases were in the 4th decade of life, and were nervous in type.

This departure from the normal run of cases, and the paucity of them, may be to some extent explained by the presence near Sunderland of Sherburn/



Sherburn Hospital, whose honorary surgeon, interested in thyroid surgery, had to some extent canvassed and drained the district. To this hospital may have gone the younger group of patients of the fair sex, whose greater interest in personal appearance may have led to earlier diagnosis and treatment.

The definitely greater incidence in women is universally accepted, it is instructive that this is also found in myxoedema. It may be dependent on the greater variations which take place in the endocrine system in women from physiological demands, e.g. puberty, menstruation and pregnancy, such demands being non-existent in man. It is almost axiomatic that these periodic variations will result in some degree of instability of the endocrine system.

Another disease with a greater prevalence in the female sex is chorea, which affects three or four times as many females as males. Chorea, like exophthalmic goitre, often has as exciting cause some emotional disturbance; probably both are related to the inherent instability of the emotional nervous system which is greater in women than in men.

The very unequal incidence in the two sexes would seem against a microbic or other infection per se. (Chorea may be a nervous concomitant of/



of the rheumatic diathesis and not due to the same exciting cause).

Another lesser point is that the sex ratio remains almost constant at the different periods of death incidence. This might be construed as evidence against any relationship between the disease and the period of active physiological sexual life.

(11)  
Williamson when showing that colloid and secretion were two distinct entities also described these two functions as having a varying preponderance with age.

In the embryo and the newly born secretion is the only product of the gland, (which contains no iodine). After birth colloid storage increases up to five years of age, and secretion declines. From 9-15 the position is reversed, secretion predominates. From puberty till 18 or 20 sex determines the picture - the female presents in the main a secretory picture, the male one chiefly of colloid storage. After that age the picture of male and female functions approximate, except in pregnancy and menstruation - these latter functions, peculiar to the female sex, must tend to greater instability of thyroid function.

May not the greater incidence in the female sex, and the large incidence of cases about the 18th and/

*Illogical*

*not "showing" but "stating"*

and 25th years, be partly explained on this basis?

Grave's disease is almost entirely a secretory picture. May not the thyroid overstepping all bounds pursue its secretory career in a manner analogous to the growth of malignant tissue to the almost total exclusion of colloid storage?

*Too much  
arm chair  
surmise*

### 3. Family Predisposition.

There is a general consensus of opinion that the condition may have a family predilection. The condition has even been observed in three successive generations. Oesterreicher's classical case is that of a mother with ten children, eight of whom suffered from exophthalmic goitre, and one of the latter had three children thus affected.

Letheby Tidy and others agree that exophthalmic goitre is more common in families where hysteria and other nervous conditions are found. This would lead to the theory that exophthalmic goitre and instability of the nervous system may be related.

In the writer's <sup>series</sup> exophthalmic goitre was observed in two sisters; one sister, unmarried, was a severe case, the other, a widow, was not so. Another patient in the series states that her mother had a goitre and protruding eyes, and her family doctor confirmed the statement.

A history of "nervousness" in the family was given/

given by rather less than half of the cases.

#### 4. Marriage.

Whether marriage has any effect or not on the disease incidence is as yet unknown, though Campbell has shown statistically that the condition is three or four times more common in the unmarried.

In this series 22 cases were married and 28 unmarried; 7 out of the 8 male cases were married, thus leaving 15 married and 27 unmarried female cases. It is deemed unwise to draw any inference from these figures.

#### 5. A human disease.

While goitre is widespread throughout the animal kingdom, from fishes to man, exophthalmic goitre is rarely reported apart from the human subject.

(12)

McLean, however, reports an epidemic of exophthalmic goitre occurring in 1915 among the lambs on a farm 14 miles from Winnipeg. In a herd of 400 sheep, apparently normal, 70% of the lambs were born with the symptoms of exophthalmic goitre, and of these 50% died; the majority of those able to nurse recovered. The thyroid glands examined histologically revealed the picture of true Grave's disease. There is no parallel in the human subject.

The/



The equivalent of exophthalmic goitre is believed  
 (13)  
 by Pugh to exist in cows under the diagnosis  
 nymphomania - it is a form of mental distress  
 found when the calf is removed - it may also be  
 found after too prolonged lactation.

## 6. Geographical.

Exophthalmic goitre is widely distributed throughout the world and special prominence is given to it especially in the American medical press, where it is apparently much more common than in this country.

But surely nowhere is it more common than in  
 (14)  
 certain districts of Silesia. Simon reporting  
 on the result of a commission on the subject of  
 goitre in Silesia, states that the extent of goitre  
 is enormous - even exophthalmic goitre has an  
 incidence of from 1-50% in certain districts; for  
 this amazing fact the commission could assign no  
 cause.

Campbell found in England and Wales that the  
 death rate was greater in the country than in the  
 towns, and greater in the towns than in the cities;  
 in London it was the least of all. He suggests  
 that this represents a real difference in incidence,  
 and not merely in fatality. On his reckoning  
 exophthalmic/



exophthalmic goitre is nearly twice as common in the country as in London.

This would be a rather difficult statistical investigation, but <sup>if</sup> Campbell's figures are to be accepted, it would seem impossible to reconcile them with any theory on the stress of modern life.

It may be mentioned here that the water supply was investigated in every case in the writer's series. It was found impossible to draw any conclusions as to the greater prevalence of the condition in hard or in soft waters, in water which was exposed in the country or in the ordinary town's supply.

#### 7. Nervous Shock and Strain: Fright.

A history of nervous shock or strain is found in so many cases that it cannot be neglected as an etiological factor. The symptoms have come on suddenly after severe fright, and all the classical features <sup>have</sup> been seen within two months of the onset; on the other hand they have come on insidiously, following the strain of years, usually that of worry or grief.

That tachycardia and palpitation, trembling, protrusion of the eyes, cold clammy sweat and diarrhoea have been produced by emotional disturbance is well known. That emotional disturbance can produce/

*This not pure.  
What is your  
valuation of the  
figures? Are there any  
ballasts in them?*

produce a swelling of the thyroid is not so well known, though the fact that sometimes the neck of the adult female becomes swollen under excitement was known to the ancients. An old marriage custom in the South of France was for an old woman to circumscribe the bride's neck with a piece of string on her wedding eve, and if the string failed to meet in the morning, coitus was deemed to have occurred.

(15)

Cannon's work on the physiology of anger, fear and pain is very illuminating. He states that any degree of excitement in the central nervous system, whether felt as anger, terror, pain, anxiety, joy, grief, or deep disgust, is likely to break over the threshold of the sympathetic division and disturb the functions of all the organs which that division innervates. Various strong emotions can thus be expressed in the diffuse activities of a single division of the autonomic nervous system, e.g. the division which accelerates the heart, inhibits the movements of the stomach and intestine, contracts the blood vessels, erects the hair, dilates the pupils, causes trembling of the muscles, liberates sugar and discharges adrenaline. These clinical phenomena immediately suggest the picture of exophthalmic goitre.

Crile/

(16)  
 Crile says in support of the factor of nervous strain. "I have never known a case of Grave's disease to be caused by success or happiness alone, or by hard physical labour, unaccompanied by mental strain, or to be the result of energy voluntarily discharged."

The effect of the war on the incidence of the disease seems marked. From the first graph a steadily increasing post-war death rate is seen. This was prophesied by Hector Mackenzie (17) in 1916 in these words: "Grief and anxiety are weighing down the hearts of countless mothers, wives and sisters. While the women of this country have shown a fortitude and endurance beyond all praise, it cannot but happen that the ordeal which they have gone through, will produce in some more than a passing effect on the emotional nervous system. I think we shall undoubtedly see in the future an increased number of cases of exophthalmic goitre."

While Rogers states that there was no case of exophthalmic goitre after the battle of Jutland, Leon Berard (18) met with a relatively larger number of cases in men between 20 and 45. He quotes three cases which came on suddenly, following violent emotion and exertion. In a few days there were large goitres, exophthalmos, nervousness and anxiety, diarrhoea and loss of weight.

He believes that nervous shock, manifested essentially in vasomotor disturbances, and transient or permanent changes in the ductless glands and central nerve cells was the starting point of these cases.

(19)

Bram states that the term shell shock has been applied to sufferers from various primary obscure conditions, of which 65 per cent. later develop all the ear marks of exophthalmic goitre.

Whether modern life in itself is not a strain seems to warrant serious consideration. Bram (20)

says "The present high tensioned mode of existence, accompanied as it is by the rush to earn the dollar, and often the greater rush to spend it, long waking hours and diminished sleep, the frenzy for exciting forms of avocation and recreation - all these in lowering body resistance and diminishing somatic stolidity, reduce the threshold of nervous reaction, which is the strongest predisposing cause of Grave's disease."

(21)

Pfeiffer believes that every case of exophthalmic goitre of emotional origin is syphilitic in nature.

In the writer's series emotional disturbance seemed to be the main etiological factor in about one-third of the cases. Syphilis appeared to play no part; the Wasserman was taken in 41 cases, and in/



in no single instance was it positive.

A kitchenmaid developed the condition after having been bitten by a fox-hound which had entered the kitchen; a pit-head worker developed the disease after seeing a man smashed in a pit-head accident; another girl after seeing her mother killed in a street accident. A burglar entered the bedrooms of two other girls, and one girl got a bad fright by the entrance of a stray cat during the night. All three confessed to being afraid to sleep at night after this, and later developed exophthalmic goitre. Lastly one woman attributed her condition to the fright she had received in Paris in a taxi!

There were many varieties of strain given in the histories - that of uncongenial employment and long hours, that of unhappy married or unhappy home life, the strain of months of nursing at her child's sick bed, the fear of rats in a girl working in a bakehouse, the strain of financial instability and the fear of unemployment, and that of coitus interruptus. One girl developed the condition after being jilted by her sweetheart. Lastly one girl at the age of fifteen was left in the house by herself one night. When her mother came back she found her lying on the floor in a faint and the girl was aphasic for about five hours - within twelve/

twelve months she had developed all the symptoms of the disease.

#### 8. Infection.

Infection is considered by some as an important etiological factor, by others as the actual cause of the disease.

(22)  
Moebius in enumerating the possible causes of Grave's disease, mentions polyarthrititis, typhoid and influenza and in rare cases scarlet fever, measles, malaria, syphilis, and other infectious conditions.

(23)  
Kocher believes that the condition may occur through rheumatism, influenza, angina, scarlet fever, measles, diphtheria, typhoid, pneumonia and syphilis.

(24)  
Howard in summarising the results of investigations undertaken in U.S.A. remarks that "coryza, sinusitis, tonsillitis and other acute infections such as influenza, frequently precede the symptoms of exophthalmic goitre."

(25)  
Kaplan states that there is a general consensus of opinion as to the importance of sepsis, especially tonsillar and oral sepsis, and intestinal toxæmia in the etiology of exophthalmic goitre. To these Campbell adds rheumatic fever and chorea and Maranon (26) stresses the importance of influenza/

influenza which he considers has not attained the prominence it deserves.

(27)

Jennings reported two cases of measles in patients with Grave's disease; one patient died the other, previously mild, got so very rapidly worse, that operation had to be performed. This shows the deleterious effect of infection on the conditions.

Lastly Pfeiffer has stated that he is convinced that every case of exophthalmic goitre of emotional origin is syphilitic in origin.

In the human subject a careful examination will reveal either a focus of infection or a history of past infection in almost 100 per cent. of cases. It is therefore easy to fall into the error of "post hoc, ergo propter hoc", and still easier when one is endeavouring to draw conclusions.

This series showed a considerable proportion of cases who gave a history of infection or were suffering from infection. Influenza (25%), septic teeth (25%), tonsillitis (25%), chorea (4%), urinary sepsis (4%), rheumatic fever (2%), constipation (10%), 6% had suffered from typhoid, and 4% specially mentioned coryza.

From most of these it was deemed inadvisable to draw conclusions. Only when a definite history of acute disease followed by the symptoms of exophthalmic goitre was given, was infection considered a definite/

definite etiological factor. Only two diseases fall into this category - influenza and tonsillitis. Syphilis was deemed to play no part in any case in the series; 41 Wasserman tests were taken, and in no case was it positive. This would seem quite incompatible with Pfeiffer's statement.

*You have missed his point that they were of constitutional origin. You have not stated the facts necessary to test his assertion.*

#### 9. Dietetic Factors.

The question of the influence of diet in the treatment of this condition has brought to light certain interesting facts.

(28)

McCarrison has shown that an excess of fats or of unsaturated oleic acid in the diet may cause a relative deficiency of iodine and enlargement of the thyroid gland, and it has been suggested that fats should be reduced in these cases. Chalmers Watson has shown that a meat diet produces changes in the thyroids of animals suggestive of hyperthyroidism.

(29)

Professor and Mrs Mellanby found in their work on experimental rickets that when butter was excluded in the diet a fivefold increase in the size of the thyroid took place, but this was not found when cod liver oil was given instead of butter. They have found that in cases of Grave's disease the addition of butter intensified the tachycardia/

*When? where? reference?*

*X?*



tachycardia and nervousness and was followed by loss of weight.

Further investigations would seem necessary before these results can be wholly accepted, for it does not necessarily follow that a diet which induces hypertrophy of the gland in healthy animals will have the same effect in human patients with Grave's disease.

*rather muddled*

10. Associated with Secondary Growths.

(30)

Mori records three cases in which Grave's disease developed because of secondary growths in the thyroid. The primary growths were a sarcoma of the pelvis, a melanotic sarcoma of the eye, and a carcinoma of the breast.

The secondary deposits were small and there was no proliferation evident, as in ordinary Grave's disease. The author thinks that the secretion was dammed up by growths and the excess was escaping into the circulation.

11. Associated with exposure of the ovaries to radium

(31)

Ujima reports a case in which he believes typical exophthalmic goitre followed a single exposure of the ovarian region to the influence of radium. The girl had been curetted for menorrhagia at/

at the age of 13, without improvement, and two months after exposure to the radium she had the typical symptoms of exophthalmic goitre. Exophthalmic goitre has, on the authority of Bandler and Bardachzi, been observed to accompany genital hypoplasia and to follow oophorectomy.

### Theories on Exophthalmic Goitre - its Pathogenesis

#### (1) The Theory of Hyperthyroidism.

Moebius in 1886 was the first to suggest that exophthalmic goitre was due to an excess of secretion produced by the thyroid. Until recently this was regarded as the most probable theory, but it is now both on theoretical and clinical grounds giving way to that of dysthyroidism.

Thyroid secretion, either as thyroxine or as thyroid extract given experimentally in the normal human subject or in animals, will not produce all the characteristic features of exophthalmic goitre. It will certainly produce many of them, but it fails to show the exophthalmos, the stare, and the characteristic nervous phenomena. Moreover, the test specific for thyroid hormone, i.e. the acceleration of the metamorphosis of the tadpole, is negative for both normal and exophthalmic blood (Schafer).

This/

This means that there cannot be a great excess of thyroxine in the blood of the exophthalmic patient, but it does not negative increased activity or increased secretion which may be of perverted character. On the other hand this "specific" test cannot but be regarded as a very crude one, when one considers that the amount of thyroxine in the normal adult tissues is only 14 mgms., and that the daily output of the normal thyroid is only about 0.33 mgms. approximately (Plummer).

*The test is of no value concerning this argument*

## (2) The Theory of Dysthyroidism and Hyperthyroidism

### (a) The theory of Moebius.

Since the theory of hyperthyroidism failed to be conclusive, Moebius in 1896 suggested the theory of dysthyroidism - that exophthalmic goitre was caused by a secretion not only excessive but also perverted.

In both these theories Moebius believed that the cause was within the gland. While the constancy of thyroid changes in exophthalmic goitre is universally admitted, it does not follow that the origin of the condition is within the gland.

*Badly put*

(32)

### (b) The theory of Plummer

It is known that a large part of the normal thyroid can be resected before diffuse hypertrophy of/



of the remnant occurs, though it continues to deliver the normal amount of thyroxine. From this it is evident that (1) diffuse hyper~~at~~rophy of the thyroid means intensive stimulation and that (2) excessive stimulation of the normal thyroid should cause a state of hyperthyroidism before diffuse hyper~~at~~rophy occurs. It is self evident that a supply of iodine inadequate for thyroid function will cause a state of hypothyroidism and result in intense and prolonged stimulation; from this step Plummer evolved the first part of his theory - that intense and prolonged stimulation of the primarily normal thyroid, with a relatively inadequate supply of iodine compared with the stimulation, will cause the delivery of an abnormal product.

Plummer therefore believes that the causal condition is extrinsic to the gland.

That new tissue may develop in an organ under stimulation is a common observation, but that this new tissue should elaborate a product far in excess of the organism's need, as seems the case in the thyroid, is unique.

In 1912 Plummer evolved the second part of his theory. He offered the hypothesis that the condition of toxic adenoma was due to an excess of normal thyroid secretion, whereas in the case of exophthalmic goitre the ocular findings, the nervous phenomena/



phenomena and the tendency to the crisis state are caused by an abnormal thyroid agent or agents, and that the clinical entity of exophthalmic goitre varied with the ratio of the normal and abnormal products.

In 1914 Kendall isolated thyroxine, and in 1917 discovered its empirical formula, and proved it to contain 65 per cent. of iodine.

Plummer therefore carried his theory one step further and suggested that the abnormal product might be an incompletely iodised molecule driven off from the thyroid by the intense stimulation. On this hypothesis the ratio of normal to abnormal products will depend on the intensity of the stimulation and the amount of iodine present.

This theory received further impetus when Plummer made his notable discovery of the use of Lugol's iodine in the pre-operative treatment of the condition. Previous to this the general conception had been that in exophthalmic goitre the body tissues were saturated with iodine elaborated by the gland. Hyperthyroidism and hyperiodism were spoken of synonymously and so iodine seemed contra-indicated.

Plummer's theory concisely expressed now stands, that exophthalmic goitre is caused by intense stimulation/

stimulation of unknown origin, acting on the entire thyroid gland and driving it to the point of producing an active agent, abnormal both in quantity and quality, which in the tissues of the body produces the characteristic changes of Grave's disease.

That the abnormal agent might be an incompletely iodised molecule seems possible - iodine is given in the treatment in the hope of completing the iodisation. Plummer also believes that the syndrome varies with the relative amounts of completely and incompletely iodised molecules of thyroxine.

*Butter have left  
this out or say more*

(33)

(c) The theory of Scott Williamson.

Scott Williamson also holds that exophthalmic goitre is a condition of secretory dysthyroidism. He believes that there is a true secretion by way of the lymphatics which contain no iodine and is the intoxicative factor in Grave's disease, while the stored colloid material contains the iodine in thyroxine form.

In the Arris-Gale Lecture (1925) among other preliminary facts he states that two processes occur in the normal thyroid gland - secretion which is active, and colloid storage which is passive and he points out that secretion and colloid are distinct entities. This colloid probably acts as a carrier or vehicle like the glycocholates and taurocholates of/

of the bile, and just as only the excess of bile is stored in the gall bladder, so only the excess of colloid is stored in the thyroid. He also postulates that the excess of secretion may be stored in the thymus, parathyroids and possibly in the lymph nodes.

From the histopathology he divides the disease into three stages:-

- (1) an exophthalmic stage
- (2) a stage of thyrotoxicosis with exacerbations
- (3) a stage of thyrotoxicosis without exacerbations and leading to atrophy and exhaustion.

In the first stage the tissue is in a state of secretory activity in which colloid storage is absent. Since on physiological grounds colloid circulation is necessary for balanced action of the thyroid, then secretion produced in the absence of colloid cannot be normal and cannot exercise its normal effect. The action of such secretion is unphysiological, i.e. the condition is one of secretory dysthyroidism.

Boothby suggests that this lack of colloid storage may be due to lack of available iodine, with which colloid is admittedly associated.

In the second stage the follicles are being filled, in fact choked, with secretion. This choking of the follicles probably means forcing of secretion through unusual channels, eg. the blood vessels/



vessels instead of the lymph stream. Williamson suggests that this stage is analogous to the choking of the bile passages of the liver in jaundice, and to the choking of the kidney of parenchymatous nephritis which occurs in uraemia.

Clinically the exacerbations represent the addition to the exophthalmic state of a thyrotoxicosis the result of regurgitation of secretion from choked follicles, possibly into the blood stream instead of the lymph stream.

In the third stage a diffuse fibrosis of the walls of the sinusoids circumscribes the follicles like an impermeable membrane; the blood capillaries, however, lie between the fibrous wall and the epithelium and so the evacuation of secretion becomes impossible through normal channels. The choking of the gland unit becomes irreversible. Consequently there is a continuous thyrotoxicosis without exacerbations.

It is in this stage that surgery does good by extirpating large masses of gland substance containing pent up vicious secretion bound up in fibrous capsules - it relieves the body quickly of what nature is doing slowly by atrophy and exhaustion of the epithelium.

Such is Williamson's original theory of the part played by the thyroid gland in exophthalmic goitre/



goitre. Of the cause of the condition he offers no opinion save that it is a stimulus almost certainly extrinsic to the gland. This stimulus is overwhelming, colloid disappears from the gland, and later becomes inadequate to serve the body functions. In the beginning the body utilises all the secretion - later it fails to do so, and secretion becomes pent up in the follicles, and the excess overflowing exercises a toxic effect.

### (3) The Theory of Dysthyroidism and Hypothyroidism.

Because of the low iodine content of the gland and because of the success following iodine exhibition in the pre-operative treatment of the condition, it has been suggested that the disease is due to a combination of dysthyroidism and hypothyroidism. It seems feasible that a supply of iodine insufficient for thyroid function would cause a state of hypothyroidism and consequent stimulation and that abnormal products would result from this.

This theory does not receive much support; some say that operative treatment, which is removing an excess of secretion, definitely renders it untenable. On Scott Williamson's thesis the outlook is quite changed. More will probably be heard of exophthalmic goitre from this point of view in the future.



Temanite says:

"Fear came upon me, and trembling, which made all my bones to shake....the hair of my flesh stood up."

And Elihu says:

"At this also my heart trembleth and is moved out of its place".

The Psalmist plaintively laments:

"I am feeble and sore broken, I have roared by reason of the disquietness of my heart. My heart panteth, my strength faileth me. My heart is sore pained within me. Fearfulness and trembling are come upon me, and horror hath overwhelmed me."

In these passages we see a reference to the protrusion of the eyes, the trembling, the palpitation, and the loss of strength, which make up the picture of exophthalmic goitre.

Freud believes that the anxiety neurosis is sexual stimulation which is unable or is not allowed to follow its natural course, leading either to physical gratification or even to conscious desire for this. Consequently desire is repressed into the unconscious by its opposite, fear. That this may be true is more than possible, when anxiety neurosis is brought on by coitus interruptus and by the use of pernicious devices for the prevention of conception.

Stoddart states that though the disease so closely resembles the anxiety neurosis, it is rarely/

rarely caused by exactly the same etiological conditions. The usual sequence of events appears to be "(1) a fright, worry or anxiety induced by some incident or circumstances which symbolise sexual aggression; (2) partial or complete repression of the incident or circumstances, whereby the fear is left unattached, and therefore liable to attach itself to any transitory situation; (3) partial or complete repression of the fear, which then finds expression in the symptoms of exophthalmic goitre, which are nothing more than the physical accompaniments or bases of fear. "

Stoddart quotes the case of a girl of 11, whose surrogate father told her to look under the bed each night to see if a man were there. Fear was present at first during the night, and then during the day as well. At the age of 15 fear disappeared and was replaced by exophthalmic goitre in a very severe form - the patient died six months later.

The chief mental symptoms are those of a general emotional tone of anxiety or apprehension, and the physical signs are those of a normal person experiencing the emotion of fear.

Finally Stoddart says that psycho analysis reduces the pulse rate to normal in 4-6 weeks.

There are therefore distinct resemblances between/



between exophthalmic goitre and the anxiety neurosis. One case in this series volunteered the information that being already the father of five children, he had been practising coitus interruptus for some time, and that lately his mind had become obsessed with the thought that he had been guilty of an unnatural act. This was the sole <sup>event that may have been a</sup> etiological factor discovered in the case; it would seem probable that it had a direct bearing on the condition.

But while emotional disturbance seems to be the starting point in a considerable number of cases, it must be admitted that no such cause can be traced in many cases of the disease; also that many people live under emotional strain or have severe frights, who do not develop the condition (e.g. the forces in the late war).

Consequently this theory cannot satisfy all cases.

#### (5) The Theory of Sympathetic Irritation.

Many of the symptoms of Grave's disease are essentially those of sympathetic irritation - in this stimulation the thyroid and probably other glands of internal secretion are involved. Tachycardia and palpitation, exophthalmos and dilatation of the pupil, hyperglycaemia and hypochlorhydrea are all physiological results of sympathetic stimulation.

The/

The importance of the sympathetic in the pathogenesis of the disease has been confirmed by Cannon's observation that when the phrenic nerve is anastomosed to the cervical sympathetic in the cat, the animal suffers from all the symptoms of exophthalmic goitre.

(35)  
Wilson and Durant found degenerative changes in the cells of the superior cervical ganglion of the sympathetic in 16 patients with fatal exophthalmic goitre, and Wilson (36) claims to have produced the condition by injecting the superior cervical ganglion in animals with bacteria.

(37)  
W.L. Brown contends that in Grave's disease there is always underlying sympathetic irritation producing hyperthyroidism. This in turn increases the sympathetic response, and so a vicious circle is formed. Once the thyroid has been started on its evil course through sympathetic stimulation, the emotional agitation is kept up and may end even in the psycho neurosis and insanity.

(38)  
Herman Johnson states that the picture of sympathetic stimulation as shown by Cannon cannot be ignored. The sympathetic is the servant of the emotions, occasionally their master; it rules the ductless glands and is ruled by them; it may be depressed by bowel toxins and its faulty action may result in their formation. Thus a vicious circle/

Reference

circle is formed.

According to the theory of Scott Williamson the secretion of the thyroid comes into relation with the sympathetic nervous system possibly in the parathyroids, which he claims store the secretion and which have a very special sympathetic supply. Should this assumption hold good, the sympathetic irritation and the thyroid secretion seem excellently situated for the production of a vicious circle.

In our present knowledge of the sympathetic nervous system, which is still in its infancy, it is impossible to be dogmatic; but there appears to be definite evidence to show that the sympathetic is in some way involved in Grave's disease.

#### (6) A Pluriglandular Disorder.

This would seem a safe assumption on the grounds that when one of the endocrine systems is affected, the endocrine balance is upset and the other glands share in the unbalance.

(39)

According to Serdjukoff a certain amount of physiological enlargement of the thyroid gland commonly occurs at puberty, and periodic changes in its size are often associated with menstruation. Grave's disease also frequently manifests itself at or soon after puberty, when it is due to pronounced modification

Poor

X

X

What does this mean?

modification of the function of the gland. At and after the menopause there is atrophy of the endocrine glands, the whole endocrine system is re-organised, and ill balanced action often results, leading to such manifestations as goitre, myxoedema, Grave's disease, acromegaly and obesity.

The two endocrine glands most discussed other than the thyroid are the adrenals and the thymus.

#### The Adrenal Gland.

The physiological action of adrenaline is that of excitation of the sympathetic nervous system; consequently the exophthalmos, the widening of the palpebral fissure, the tachycardia and the relatively high systolic blood pressure, could be explained by an increased output of adrenaline into the blood.

(40)  
While A. Fraenkel states that he was able to show that the adrenaline content in exophthalmic blood was 4-8 times the normal concentration, Schafer states that he is unable to prove the existence of adrenaline in the blood at all; he attributes the symptoms not to excess of adrenaline but to sympathetic excitation.

Fraenkel's experiments would therefore need confirmation.

(41)  
Barr on the other hand believes that the relatively/

could be (are they?)

Not much  
use what some  
people believe



relatively low diastolic blood pressure and the dark pigmentation of the skin are due to a state of hypo-adrenalism.

(42)  
Scrimger points out that both thyroid secretion and adrenal secretion sensitise the sympathetic to the action of each other, and each stimulates the other to secretory activity.

Whether the adrenal gland is hyperactive in this condition is unknown; on the authority of Schafer the probability is that the physiological action of adrenaline is produced through the sympathetic nervous system.

#### The Thymus.

Exophthalmic goitre is usually associated with enlargement of the thymus, and some authors claim that it produces certain symptoms of the disease.

On the theory of Scott Williamson, it is the reserve store for thyroid secretion. That it does play some part in producing the symptoms (43,44) would seem probable if it is true, as Haberer asserts, that better results are obtained surgically if the thymus is removed along with the large part of the thyroid, than if the thyroid is removed alone. (45) Bircher claims even to have produced the disease by implanting normal human thymus/

thymus into the peritoneum of dogs. In view of the great difficulty in getting heteroplastic grafts to take, these experiments would seem to need confirmation.

No satisfactory explanation has yet been given of the relation of the persistent enlarged thymus to the disease.

*Is it persistent or regrowth?*

#### The Ovary.

(31)

Ujma reports a case in which he believes typical exophthalmic goitre followed a single exposure of the ovarian region to the influence of radium. A girl had been curetted at the age of 13 without improvement, and two months after the exposure to radium she had the typical symptoms of exophthalmic goitre.

Exophthalmic goitre has on the authority of Bandler and Bardachzi, been observed to accompany genital hypoplasia and to follow oophorectomy.

That the other endocrine glands are affected in exophthalmic goitre seems probable.

*Poor*

#### (7) A neuroglandular disorder.

(47)

Many people, including Wilson believe that exophthalmic goitre is not a thyroid disease but a neuroglandular disorder. Inasmuch as this theory is a composite of certain of the others, it carries the more weight.

(8)/

(8) The Theory of Infection.

Since the work of McCarrison and Farrant there has been no doubt but that a contagium vivum plays an important part in the diseases of the thyroid gland. Infections of any part are known to have a deleterious effect on the thyroid, and infections have been given an important position in the etiology of Grave's disease.

Leonard Williams believes that Grave's disease is due to a toxæmia in which all members of the endocrine hierarchy are involved.

(47)  
Farrant from a study of 85 English cases suggests a link between simple and exophthalmic goitre. He thinks that the primary cause is a bacterial toxæmia, either from drinking water, or pyorrhoea alveolaris, or from the lung or intestine or elsewhere. He believes that the toxæmia may produce no changes at all, or may stop at simple goitre, or may go on further to exophthalmic goitre, either at once or after having been simple for some time. The cure is that of the toxæmia, and in his opinion it is for this reason that exophthalmic goitre is believed to undergo spontaneous cure.

(48)  
Harries believes that exophthalmic goitre is associated with an excessive absorption of tryptophane/

tryptophane from the intestine, caused by an absence of indol producing bacteria; he finds indican absent from the urine in this condition.

Wilson claims to have produced the disease in goats by injecting bacteria into the superior cervical ganglion.

Bacteriological investigations of the thyroid gland tissue serve to confirm the infective theory.

(49)  
Gilbride in 1911 made a bacteriological study of 14 cases of goitre and isolated micrococcus tetragenus from one case of exophthalmic goitre.

(50)  
Rosenow in 1914 isolated a diphtheroid non-haemolysing streptococcus from the thyroid gland in 25 out of 32 cases of goitre, chiefly exophthalmic. These organisms when injected into dogs over a long period of time produced goitre, loss of weight, and diarrhoea; in one dog there was softening, pulsation and ~~a~~bruit over the thyroid, and tachycardia and tremor in addition.

(51)  
Lastly Cantero made cultures from thyroid tissue in 50 cases of goitre of different types and in only three cases did the cultures fail to show growth.

There is therefore evidence, both bacteriological and clinical, that infection may in certain cases cause exophthalmic goitre. It would seem almost certain, however, when one considers the universality of/  
of/



of infection, that some other factor must coexist.

(9) The Theory of Iodine on the Causation.

Early in the history of goitre Kocher made the observation that endemic goitre if treated with iodine was prone to develop hyperthyroidism. It was largely because of this observation that iodine was totally vetoed in the treatment of the condition.

Crile also believes that the improper use of iodine or thyroid products causes many cases of quiescent goitre, but especially of the adenomatous type, to be converted into hypothyroidism or to exophthalmic goitre, and Barr definitely attributes certain cases of exophthalmic goitre to the abuse of iodine. hyper

One case (case 1) in this series developed exophthalmic goitre of marked severity after treatment with both thyroid and iodine extending over a <sup>six</sup> period of months.

A consideration of the very small number of the thousands of goitre bearers, who take iodine in the treatment of their goitre with or without a doctor's care, and who become affected with exophthalmic goitre must show that some other factor does exist.

(10) The Diathesis Theory.

None of the previous theories are complete or wholly satisfactory in themselves. It is obvious that all people suffering from oral or tonsillar or intestinal infection, and that all people living under conditions of stress and strain and of emotional conflict, do not develop exophthalmic goitre, neither do all those indiscretely treated with iodine or thyroid.

Some other factor must exist; the possibility of a diathesis has been suggested.

(52)  
Eason believes that the liability to exophthalmic goitre is remote in those of strong physical build, and in those with a stable nervous system, the disease being prone to occur in those of a neurotic tendency. He points out that primary exophthalmic goitre occurs chiefly amongst women of narrow frame, of light skeletal structure, with associated narrow subcostal angle and enteroptosis. Next in frequency it occurs in men of this type, less frequently in women with stout bones and broad frame, and scarcely ever in strong virile men.

(25)  
Kaplan infers something the same in stating that he regards Grave's disease as essentially feminine in incidence and that male cases nearly always show some physical trait of feminism.

Others/



Others believe that the diathesis of exophthalmic goitre is closely related to that of status lymphaticus.

There is therefore some evidence to believe that a diathesis does exist, linked up in some unknown manner with an unstable nervous system, a gracile rather than a heavy build, and an imbalance of the ductless glands, though even this composite would seem a purely tentative one.

*you have not  
mentioned "evidence"  
only "opinions"*

III - PATHOLOGY.



### III. Pathology.

This section will be dealt with briefly, as this thesis is in the main clinical.

#### Macroscopic Appearance of the Thyroid.

The gland is enlarged in nearly all cases, though some have been described where this was not so. The enlargement is as a rule uniform, though it is quite common to find the right lobe larger than the left. The thyroid is unusually vascular and may show lobulation. It is firm in consistence and of a dense opaque meaty consistence.

*Pathologists find nothing of the sort*

#### Microscopic Appearance of the Thyroid.

The histological picture is one of hyperplasia and glandular activity.

The gland is greatly enlarged and the alveoli are numerous and are arranged irregularly.

The stroma shows, in addition to great vascularity, definite collections of lymphoid cells.

The epithelium lining the alveoli has changed from cubical to tall columnar epithelium, and the nuclei show irregularity of size and staining properties.

Such proliferation has taken place that the lining membrane has been thrown into folds, and papillae, thus formed, project into the interior of/

of the alveoli, making them look smaller than they really are, and in extreme cases causing the lumen to disappear.

The content of the alveoli is poorly staining secretion, i.e. the colloid is very markedly reduced, and since the iodine is in direct proportion to the colloid present, it is also small in amount.

This has long been regarded as the true histological picture of exophthalmic goitre, but it is not a constant picture. It is that which is found as long as the causative stimulus is working, and the gland is responding by hypertrophy and hyperplasia.

When the stimulus is withdrawn, degeneration ensues, and the hyperplastic alveoli become filled with colloid, and only a few atrophic papillae may remain as indication of the former picture.

Some specimens may show both pictures in different parts, the second picture being often well seen after ligation of the thyroid arteries; it may also be found after iodine therapy.

Scott Williamson presents original views on this subject in the Arris and Gale Lecture, 1925. These views can only be dealt with briefly - a detailed account is given in the British Journal of Surgery, January 1926.

Anatomy.

Williamson no longer regards the thyroid as a collection of independent follicles. His unit consists of "an endothelial lined cavity enclosing coiled columns of epithelium accompanied by a basket work of capillaries. These capillaries enter the endothelial sac at its hilum, where they take origin in the intralobular capillaries. The endothelial sac itself is an extension of the pervascular lymph channels which accompany the intra-lobular capillaries. The sac thus encloses a lymph space - it may be called a lymph sinusoid."

This endothelial sac is not always a mere potential space - it is often filled with thin non-colloid lymph-like matter, and frequently with lymphocytes. These contents can be traced to the lymph channels within the lobules, and then to the intralobular lymphatics and from there to the hilum of the gland.

These gland units are grouped together by strands of connective tissue into lobules. These lobules have no true blood vessels in them - only endothelial capillaries. In the centre of the lobules is a central lymph channel common to all the contained gland units.

There is also a definite lymph system which emerges at the hilum of the gland and proceeds over/

over the antero-lateral surface of the trachea into the thymus; lymph and migrating lymphocytes can be found in these passages.

Williamson has also definite views on the anatomy of the thymus and parathyroid.

He describes the thymus as an endothelial gland, the endothelium being arranged in lobes, held together loosely by a capsule, a few strands of which penetrate into the gland, and in these strands the Hassal corpuscles are seen.

The morphological picture of the thymus shows three varieties: (1) a lymphocytic type, (2) a granular or lipoidal fat type, and (3) a vesiculated fat type. These pictures have been described by Gulland<sup>(53)</sup> in the secondary lymph glands. They describe the conversion of vesiculated fat tissue into tissue bearing lymphocytes.

Williamson has shown that lymphocytic activity occurs when the thyroid gland is most active, and he looks upon the thymus as a tissue, which modifies and stores the excess of secretion of the thyroid gland.

He has also discovered two things of importance in the parathyroid gland.

(1) Under normal conditions an occasional tube of fluid lymph-like matter is found in the parathyroid. When many are found it is definitely associated with secretory/



secretory activity in the thyroid tissue. The same type of fluid and occasional lymphocytes are found in the thyroid, parathyroid, and in advanced cases continuity of this fluid can be traced from thyroid to parathyroid. He therefore believes that the parathyroid receives secretion from the thyroid. (2). The parathyroid is the site of termination of a special ganglionated branch of the sympathetic, derived either from the superior or middle cervical ganglion.

#### Physiology.

Williamson (in conjunction with Pearse) pointed out that two processes occur in the normal thyroid - one, the passive accumulation of colloid, the other the active process of secretion, and that secretion and colloid were two totally different substances.

Each function has its own histology,  
Colloid Storage - occurs in defined areas of epithelial columns, and leads to fragmentation of the columns into tense discrete spheroidal vesicles. This function is passive - the epithelium, the sinusoid, and the endothelium of the gland unit show no change.

It would seem necessary for the epithelium to evacuate the stored colloid and return to its solid/

solid form, before it is able to produce secretion.

Secretion. presents a totally different picture.

The function is an active one - the epithelial nuclei, the cytoplasm, and the capillaries all become laden with granules. These granules liquify and occupy the centre of the epithelium. At the same time the endothelial cells of the sinusoidal capillaries become laden with granules and their fluid and lymphocytes appear in the sinusoid itself and in the perivascular lymphatics.

Such secretion is not stored in the gland but passes along the lymph channels to the thymus and to the parathyroids and possibly to all the lymph-endothelial tissue. Delay in the evacuation of secretion is abnormal in the healthy gland; indeed the whole pathology of secretory activity seems to turn on the failure of the tissues to effect a natural reabsorption of the secretion.

The Applied Pathology is dealt with fully in the Etiology (page 35).

### Changes in other Organs.

Many organs other than the thyroid show almost constant changes in exophthalmic goitre, and they are apt to be overlooked owing to the more striking thyroid pathology.

### Lymphoid Tissue.

The lymphoid tissue throughout the body shows constant hyperplasia. The thymus is enlarged, and the tonsils, the Peyer's patches, and the Malpighian bodies of the spleen show hyperplasia similar to that seen in status lymphaticus.

The thymus has received the most attention while some say it is constantly enlarged, Boyd (54) finds this is by no means always so. Blackford and (55) Freligh from a study of 100 necropsies of fatal cases of exophthalmic goitre observed that the thymus was hypertrophied in all cases under forty years of age, and in half the cases over forty years of age.

### The Blood.

The blood shows constant changes - all agree that a lymphocytosis variously given as from 25-60 per cent. is found. Hammer (56) states that the blood picture is quite characteristic; the red blood/

blood corpuscles and the haemoglobin are normal; the total number of leucocytes are decreased, but the lymphocytes are doubled in number, if there is no actual lymphocytosis, a relative one is found, both the neutrophils and eosinophils are reduced. The coagulation time is retarded.

(57)  
Howard says that there is a relative lymphocytosis of 27-46 per cent. Boyd believes that a mild secondary anaemia is found, and that there is a decrease in the total number of leucocytes at the expense of the polymorpho-nuclears.

#### The Heart.

The cardiac changes are important. Briefly the cardiac pathology would seem to be cardiac over-action resulting in hypertrophy which is later followed by myocardial degeneration which causes cardiac dilatation; as the degeneration increases, there is auricular fibrillation and ultimately death.

Hashimoto has found curious bundles of cells between the muscle fibres and round the blood vessels indicating chronic non-suppurative (58) interstitial myocarditis. Goodall and Rogers have described changes in the myocardium in cases of sudden death in exophthalmic goitre - they found actual necrosis of the bundles of muscle fibres/



fibres scattered throughout the myocardium.

(59)  
In 1916 Fahr reported destructive lesions of the myocardium in five fatal cases of exophthalmic goitre. In each case interstitial myocarditis was found and the cardiac muscle fibres showed degenerative changes with infiltration of leucocytes between them and round the vessels.

It is therefore evident that the secretion in Grave's disease has a very deleterious action on the heart muscle. From the pathological point of view the nature of the secretion does not matter.

#### The Nervous System.

L.B. Wilson has demonstrated degenerative changes in the cervical sympathetic in the large majority of a small series of cases. The principal changes are excessive pigmentation of the nerve cells, chromatolysis, and finally atrophy. These findings are of great interest in view of the relation of the sympathetic nervous system to the disease.

S.A.K. Wilson claims to have found histological changes in the intermedio lateral tract of the spinal cord in seven fatal cases.

#### The Muscles.

The muscles show fatty degeneration in places/

places; this is most marked in the quadriceps femoris, and probably accounts for the weakness in climbing stairs of which some of the patients complain.

IV. /

#### IV. SYMPTOMATOLOGY.

#### IV. Symptomatology.

##### Classification.

Exophthalmic goitre is usually classified according to onset - into acute, subacute and chronic cases, and according to symptoms into complete and incomplete cases. The last mentioned class includes the "for fruste", the Basedowoid goitre, and ~~in~~ most cases of hyperthyroidism not associated with toxic adenoma.

(60)  
A.J. Walton has suggested another classification from a large series of cases. He divides his cases into two groups:

(1) Vascular Type: found in young women with large pulsating thyroids, rapid pulse, exophthalmos, dyspnoea and palpitation, but nervousness is only moderate in severity. (He believes that good results follow operation in this class.

(2) Nervous Type: found later in life in women near the menopause; the thyroid is not much enlarged, the heart symptoms and the exophthalmos not so markedly prominent, but the nervousness is very marked. (He believes that the prognosis of operation in this class is not so good).

The/



The acute cases are happily rare. Leon  
(18) Berard has reported three cases in soldiers in which tachycardia and palpitation, exophthalmos and tremors, and even large goitres developed in a very few days. This is exceptional.

Should the disease persist in its acute form, the palpitation and tachycardia become intense, and are accompanied by praecordial pain. Vomiting and diarrhoea usually supervene, and are associated with acetonuria. Glycosuria is also found. The exophthalmos becomes more pronounced, and the peculiar "glassy glitter" of the eye increases. Auricular fibrillation develops and mental symptoms usually precede the delirium, coma, and death, which supervene.

The subacute cases are those able to describe the onset of their symptoms in order, and to give their duration with approximate dates.

The chronic cases have often so insidious an onset that the patient is unaware of her condition. The first symptoms may be weakness and palpitation, loss of weight and sweating; the friends may notice that her eyes have become more prominent; but it is often left to the doctor to draw her attention to the fulness of her neck.

It is therefore evident that the disease has

a youth, that it does not spring forth fully formed like Pallas Athene from the brain of Zeus.

The order of onset of the symptoms seems to vary, nevertheless, but according to Plummer<sup>(61)</sup> they appear in this order:- Nervousness, tremor, tachycardia, goitre, exophthalmos, weakness, loss of weight, sleeplessness, diarrhoea, vomiting, mania. A more usual order is possibly tachycardia and palpitation, loss of weight, nervousness and tremor, goitre and exophthalmos.

#### The Crisis State.

Before describing the symptoms in detail it is wise to consider the crisis state. The determining factor is often influenza or operation. All the characteristics of intense toxæmia develop - as mentioned before it may be compared to the development of delirium tremens in chronic alcoholism. The nervous phenomena become increased, the patients thrash about in bed and may develop a generalised erythema, the heart is overwhelmed by toxins - it is dilated, the pulse becomes irregular, the area of hepatic dulness is increased, and albuminuria occurs - collapse is followed by anuria, fever, vomiting, delirium, coma and death. One case of crisis ending fatally has been seen by the writer.

Symptoms/

### Symptoms.

#### (1) The Thyroid.

The gland is usually enlarged, and in most cases symmetrically. In some the right lobe seems more enlarged than the left, and in these cases the exophthalmos may be more marked on the right side. It must be remembered that anatomically the right lobe of the thyroid lies more anteriorly than the left and allowance made for this.

The lobes are usually smooth and moderately soft, in very vascular cases they may even feel cystic; on the other hand, the thyroid may be unusually firm and granular, due to the irregularities caused by the hyperplasia.

An expansile pulsation may be seen and a systolic thrill felt. Various murmurs have been described, carotid murmurs and venous hums having been excluded. The most common is a systolic murmur; a continuous murmur with a systolic accentuation has also been described, and in rare cases even a diastolic murmur. Loud localised and prolonged murmurs of vibrating quality, with maximum intensity over the superior lobes of the thyroid are believed to be diagnostic of the condition. Plummer states that they are present in 80 per cent. of cases.

Pressure/

*poles*

Pressure signs in exophthalmic goitre are rare, and tenderness is almost unknown.

Goitre was present in 90 per cent. of the cases of the writer's series. The smooth and soft thyroids were found in the young and recent cases, the firmer and granular thyroids in the older cases, and in those who had undergone X-ray or iodine treatment.

The right lobe was the larger of the two in 40 per cent. of cases. In the two most severe cases (Cases 8 and 21) a condition of lobulation of the gland was believed to be felt. The right and left lobes were subdivided, the consistence was the same throughout, there being no suggestion of adenomatous formation.

The only murmur present in the gland was the systolic one except in a few cases where a continuous murmur with systolic accentuation was found. The loud, prolonged and vibrating murmur over the superior thyroid vessels was observed in many cases.

Pressure signs and tenderness were not found. Several of the cases stated that the goitre was enlarged either premenstrually or at the menstrual period.

## (2) The Eyes.

### Exophthalmos.

While/



Exophthalmos.

While exophthalmos is described as one of the four cardinal signs of exophthalmic goitre, it may in rare cases be absent. McKisack<sup>(62)</sup> records a series of twenty-one cases without exophthalmos; all had tachycardia, most had tremor, many had a slightly enlarged thyroid, but exophthalmos was absent. It is not an early sign, but is present in 70 per cent. of cases (Price).

The other important feature of the eye in this condition is the peculiar "glassy" glitter or "stare". It is believed that the more toxic the patient, the more pronounced are the exophthalmos and the stare.

The cause of the exophthalmos is uncertain. Schafer believes that it is due to a spastic condition of the plain muscle of the orbit caused by hyperexcitation through the sympathetic. Foster Moore<sup>(63)</sup>, on the other hand, ascribes it to an excess of orbital fat, and believes that this also accounts for the limitation in the movements of the eyes. Dunhill<sup>(64)</sup> points out that if patients are kept till spasm of Muller's muscle has become a contracture, proptosis will be kept up by (1) the muscle itself pushing the eye forward, and (2) the oedema produced in the orbital cellular tissues by the/

the contracted muscle, which will tend to cause further proptosis. On the theory of Plummer both the exophthalmos and the stare are the outcome of toxic products, possibly an incompletely iodised molecule of thyroxine produced by the thyroid.

The exophthalmos is nearly always bilateral and may be extreme - it may lead to lagophthalmus, corneal ulcer and even destruction of the eye. The late Mr Jessop had collected twenty-five cases of Graves' disease, in which an eye had been lost due to ulceration through extreme ptosis (quoted by Dunhill, q.v.).<sup>(65)</sup> Horder believes that should the exophthalmos be unilateral, the gland is enlarged on the same side as the eye.

In addition to the exophthalmos and the stare, various eye signs have been described - none of them are pathognomonic of exophthalmic goitre.

Dalrymple's sign. Retraction of the upper eyelid is often found, so that there is an unnatural degree of separation between the margins of the two lids, more than the protrusion of the eye can account for. This in more advanced cases exposes the sclera between the lids and the iris.

von Graefe's sign. Normally when vision is directed downwards, the upper lid moves concordently with/

with it. In this disease there is lagging of the upper lid on looking downwards, so that the sclerotic is seen above the cornea.

Dalrymple's sign and von Graefe's sign can be explained by an action of the sympathetic nervous system on the involuntary muscle fibres supplied by the sympathetic in the levator palpebrae superioris.

Stellway's sign. There is diminished frequency of winking and imperfect closure of the lids during the act.

Moebius' sign. There is imperfect power of convergence; in milder cases this may amount only to difficulty in convergence.

Joffroy's sign. If the face be inclined downwards, on looking up, no wrinkling of the forehead takes place.

Plummer has pointed out an early and very characteristic eye sign - a short stare alternating every few seconds with a quick irregular blinking of the eyelids.

Schafer states that dilatation of the pupils though not constant is not uncommon. If the sympathetic were the exciting factor in the disease, one would expect dilatation.

Paresis of some of the external ocular muscles/

muscles has been occasionally described. Pulsation of the retinal vessels is common; the optic nerves show no pathological change.

Lastly the skin of the eyelids may show dark pigmentation. Some believe this to be a sign of hypo-adrenalism - in the writer's experience it has been most marked in those cases suffering from chronic myocardial failure.

(66)

Burrows describes a very unusual eye complication in Graves' disease - that of recurrent dislocation of the eyeball in a man of 45. Thyroidectomy was followed by regression of the exophthalmos, and the dislocation did not recur.

In this series exophthalmos was present in 80 per cent. of the cases. The exophthalmos was greater on the right side in 10 per cent, though in one case there was definitely greater exophthalmos on the left side. Stare was present in about one half of the cases. It was considered that exophthalmos might be divided into two phases:

- (1) an actual protrusion of the eye,
- (2) a widening of the palpebral fissure and that ratio varied in different cases.

Corneal ulcer was observed in two cases, both males, but yielded readily to local treatment. Plummer's early sign - the short stare, alternating every/



every few seconds with quick irregular winking of the eyelids, was extremely common.

The frequency of the eye signs was as follows: von Graefe, 60 per cent; Dalrymple, 75 per cent; Stellwag, 70 per cent; Joffroy, 30 per cent; Moebius, 25 per cent.

Dilated pupils were found only in 15 per cent. of cases.

### (3) The cardio vascular system.

#### Tachycardia and palpitation.

The onus of exophthalmic goitre rests on the heart; amongst the earliest symptoms are tachycardia and palpitation, amongst the complications myocardial degeneration figures prominently, and amongst the causes of death cardiac failure stands præeminent.

Tachycardia and palpitation are often the first symptoms; in any patient with a persistently rapid pulse it is incumbent on one to suspect Graves' disease.

(67)

According to Grant tachycardia is not only one of the cardinal symptoms, but it is also an index of the severity of the case, for in his opinion the degree of tachycardia roughly parallels the/

the degree of elevation of basal metabolism.

Overactivity of the thyroid gland causes increased oxygen consumption when the body is at rest, and more so when it is performing muscular work. The heart does more work to supply the necessary oxygen; it beats more forcibly and more rapidly. Tachycardia is caused by the heart's more rapid beat, and palpitation by its more forcible beat.

Some idea of the extra work imposed on the heart in exophthalmic goitre is shown by the following calculation:-

A goitre patient whose heart is beating 120 times per minute at rest, is beating 40 times more frequently per minute than one whose heart is beating 80 per minute, i.e. in 24 hours this patient's heart is beating  $40 \times 24 \times 60$  or 57,600 more times than in the normal individual.

The heart can supply those extra beats and maintain the increased force of the contraction for some considerable time; it hypertrophies but eventually it becomes fatigued from the heavy and continuous demands on it, and symptoms of cardiac failure ensue.

An additional factor is probably present in producing the myocardial damage - the alteration in the thyroid molecule which is in itself a toxin, but/

not proved

but for practical purposes this may be neglected.

While in most cases the cardiac failure has a chronic course, acute cardiac dilatation may occur at any time; it is of serious import, and is most common in acute exacerbations.

Death may, however, take place quite suddenly, long before there is any dilatation of the heart or sign of cardiac failure. (68) Goodall and Rogers have described changes in the myocardium of such cases, and find actual necrosis of bundles of muscle fibres scattered throughout the heart muscle. This myocardial degeneration is of such medico-legal importance that in 1917 Sir Bernard Spilsbury (69) stated that "exophthalmic goitre occupies an important position as a disease liable to cause sudden death owing to secondary disease of the heart muscle..... death may occur suddenly with no apparent cause."

Goodall and Rogers offer the following electrocardiographic evidence of myocardial degeneration in exophthalmic goitre.

(1) The P wave reaches the level of the T wave either from auricular overaction, or from impaired ventricular contraction.

(2) An increase in the PR interval is present in some cases, indicative of delayed conduction in the bundle of His.

Both/

Both these findings are very suggestive of myocardial degeneration.

The exaggeration of the P. wave has also been noticed by Harris <sup>(70)</sup>, who suggests that it signifies hypertrophy of the auricle, and points out that a similar condition is found in mitral stenosis. It is significant that both mitral stenosis and exophthalmic goitre predispose to auricular fibrillation.

In this series more than a dozen electrocardiograms were taken, and no case showed any departure from the normal unless auricular fibrillation was present.

#### Physical Signs.

The heart and area of cardiac pulsation are not increased in size till hypertrophy of the ventricles has occurred. At the same time the force of the cardiac impulse is markedly increased and the shock of the heart's contraction is enormous. The heart sounds are naturally very loud, and can be heard at the posterior aspect of the chest with great ease.

The first sound is particularly loud and snapping in quality, similar to the type of first sound in mitral stenosis, and due in both cases to the/



the force of the contraction. If it is not present it betokens exhaustion of the cardiac muscle.

Systolic functional murmurs are rarely absent either at the apex or at the base of the heart. The most common of these is a pulmonary systolic murmur, which is often exceedingly high pitched, and is probably caused by the increased amount of blood, passing through the orifice.

The pulse is very rapid from 100 - 160 per minute; it is regular in force and time, and is for practical purposes a Corrigan's pulse.

Early cardiac failure was found in one half of the cases seen, and auricular fibrillation was present in 20 per cent.

When cardiac failure sets in, a slow auricular fibrillation is not uncommon in the last stages, probably from involvement of the bundle of His. This fibrillation does not yield to digitalis as a rule; but even in the presence of permanent auricular fibrillation the cardiac function may be surprisingly good. One patient (Case 23) who had had auricular fibrillation for years was quite able to carry out his work as a joiner.

Pulsation of the vessels is commonly present in the neck, and may also be seen in the vessels of the hands.

Vascular erythema is often found. It may be/

be localised to the area of the thyroid, or to an area around the thyroid; it may be found over the neck or face, or less commonly it may be generalised.

### The Blood Pressure.

In the various standard text-books there does not seem to be unanimity of opinion on the state of the blood pressure. Letheby Tidy states that the blood pressure is variable and often high; Osler's opinion is that the blood pressure varies; there may be an early stage of hypertension followed by a long period of hypotension. Stoddart states that a low blood pressure is the rule, and probably accounts for those cases in which the patient feels the pulse all over the body. This statement does not seem the least conclusive.

(41)  
Barr believes that the blood pressure is variable. He states that the viscosity of the blood is decreased and the arterioles dilated, the peripheral resistance is lessened and the capillary circulation is active. This leads to a lower mean arterial pressure, but the capillary and venous pressure rise.

There is a large supply of blood to the heart, the ventricular cavities are large and their systolic output great. With a large rapid output the systolic pressure is raised, but as the arteries are/

are large and the peripheral resistance low, there is a great fall in the pressure gradient with a relative low diastolic pressure - this condition gives rise to longitudinal straining of the arteries. A high systolic and a low diastolic pressure means a high pulse pressure; with such there is much waste of energy, the heart is overloaded, and the energy is almost totally expended during systole - none is stored; consequently the heart enlarges and hypertrophies and the vessels become elongated and sclerosed.

Crile believes that the blood pressure may show very little change except that the systolic pressure is slightly increased, and the diastolic is lower than normal; in other words the pulse pressure is increased, and Phillips corroborates this statement.

Plummer has found in a series of cases that the pulse pressure is above normal; that the systolic blood pressure is usually above normal but may be 110 or less; in the latter case the diastolic pressure is sufficiently low to give at least a normal pulse pressure. He maintains that a pulse pressure of less than 40 is sufficient to exclude the diagnosis of exophthalmic goitre.

(70)

Harris states that the systolic arterial pressure is usually increased, except when cardiac failure/

failure has supervened. In his opinion the most striking feature of the disease is that in it a rapid pulse and a high pulse pressure coexist - in any other condition a frequent pulse is accompanied by a low pulse pressure. He has also shown that digitalis increased the pulse pressure and believes that it is therefore contra-indicated in this condition.

Goodall and Rogers have studied the pulse pressure of exophthalmic goitre at length and believe that three stages exist:

(1) A preliminary stage of hypertension.

This is relatively short, occurs at the commencement of the condition, and in their opinion is probably due to peripheral vasoconstriction induced by the action of the adrenals.

(2) A stage of hypotension.

This is long, lasting over months or years; the blood pressure is below the physiological value; the lowered tension being probably due to the depressor substance secreted by the hyperactive thyroid.

(3) A stage of hypertension.

This occurs usually some years after the second stage, and may be associated with either a reduction of the excessive thyroid activity and consequent relative increase in that of the adrenal, or to/



*Thyssen ?  
Harris + Lamm*

to a secondary change in the cardio-vascular system, e.g. cardiac hypertrophy.

In the writer's series tachycardia and palpitation were present in 100 per cent. of cases. Some patients complained of inability to sleep because of these symptoms. The deleterious action on the heart was noted in many cases - hypertrophy and auricular fibrillation being common signs. This auricular fibrillation was slow, and the patients seemed in many cases but little inconvenienced with it.

The blood pressure was closely studied. The possible fallacy that a temporary increase in the systolic pressure might follow the anxiety of medical examination was nullified by repeated readings. The conclusions drawn were that the systolic blood pressure was usually raised, that the diastolic pressure was low, and that consequently there was an increase in the pulse pressure.

In a few cases, and there were as a rule those in whom the toxicity was high, the diastolic pressure was difficult to define. There was no definite end-point to the change of note - instead there was a soft shading of tone down to zero. This has been described by some American authors as the "diastolic shading".

An interesting point, noted in taking the blood pressure, was that after the application of the sphygmomanometer numerous little petechial haemorrhages could be seen in the skin; these were found in several cases, and were probably caused by rupture of distended capillaries. Appended are some of the blood pressure readings from this series of cases:-

Blood Pressure

Case	Systolic	Diastolic	Pulse Pressure
1	150	68	82
2	150	70	80
3	140	90	50
4	155	70	85
5	170	98	72
6	150	108	42
7	140	70	70
8	167	80	87
9	136	70	66
10	138	60	78
11	135	74	61
12	140	72	68
13	175	80	75
14	120	76	44
15	160	68	92
16	160	68	92
17	140	65	75
18	154	80	74
19	120	60	60
20	150	82	68

Rest alone,<sup>or</sup> rest with iodine therapy, was found to cause a definite fall in the systolic blood pressure, the diastolic was as a rule little affected.

For example:

Case/

Case 10 - Rest.

8/9/25	138 S.	60 D.
14/9/25	118 S.	52 D.
18/9/25	108 S.	52 D.

Case 16 - Rest.

24/8/25	160 S.	68 D.
28/8/25	146 S.	62 D.
21/9/25	134 S.	64 D.
8/9/25	132 S.	60 D.
13/9/25	128 S.	60 D.
18/9/25	124 S.	60 D.

Case 1 - Rest iodine.

21/10/25	158 S.	68 D.
27/11/25	146 S.	68 D.
22/12/25	138 S.	66 D.
11/1/26	130 S.	62 D.

Case 2 - Rest iodine.

28/1/26	148 S.	70 D.
8/2/26	130 S.	60 D.
20/2/26	126 S.	60 D.
12/3/26	120 S.	70 D.

Another feature is that the pulse may show extreme instability. The graph from case 1 shows the extrinsic causes which results in an unstable pulse; that from Case 10 also shows instability. The patient was toxic and very wilful; leaving the ward one hour, wishing to remain in half an hour later - she ultimately did go home without due notice of her immanent departure.

Graph 3. /

Graph 3.

Pulse Rate.

50 70 90 110 130

Graph 3.

B.M.R. taken. ← →

B.M.R. taken ← →

Unleashed on. ← →

B.M.R. taken. ← →

Insulin started ← →

Blister expd. ← →

B.M.R. taken. ← →

Time in days.

1 day = 1/10"

Xmas day →  
 other hospital  
 festivities ↓

going home ← →

Trace 1.  
 Helen's hmg. act. 16.

Pot. 100. gr 1/10

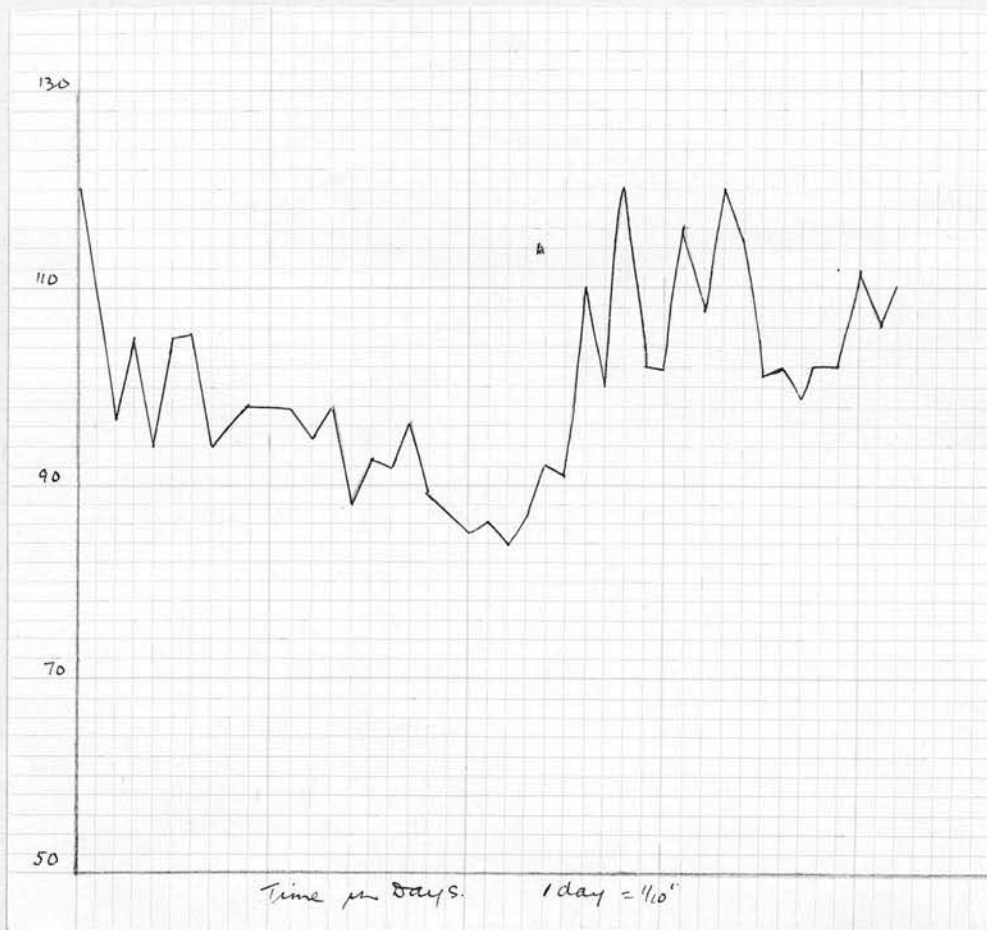
Instability of Pulse.  
 Cause

Pot. 100. gr 1/10

No. Pot. 100.

Pot. 100 gr 1/10





Graph 4.

Case 10 - Instability of pulse.

(The mean of 2.12 hrly. readings is used).

(4) The Nervous System.

Tremor is given as one of the cardinal signs of the disease. It is an index of the degree of toxicity, being absent in mild cases. The tremor is best seen in the fingers, and more so when the arms are held forwards and the fingers extended; the tremors are very fine, and at the rate of 7-10 per second. They were first described by Basedow.

Emotional Tone. While the emotional tone is usually regarded as one of anxiety and apprehension, this view would seem to need some qualification. Several cases states that they were irritable and bad tempered on very little provocation. In mild cases the nervous irritability is evidenced by the patient's extreme restlessness - she shifts her gaze rapidly from one object to another, and makes useless but semi-purposeful movements of her hands, e.g. smoothing her dress, buttoning and unbuttoning her coat. In a patient with marked restraint, these features may be suppressed and an air of extreme tension be found instead. When the patient talks unusual animation is often evidenced in her excessive speech, her frequent gestures, her mobile features and snapping eyes. Her conversation is sprightly, and her whole outlook optimistic; a supreme self-confidence is present, e.g. re-operation.

This/

*Sincerely not*

This is in definite contrast to the mental attitude in the anxiety neuroses. These patients may be a little diffcile, slightly wilful and desirous of their own, not their doctor's, way. Case 10 was typical of this, going home one hour, apologetic the next, undecided shortly after this; she did end by leaving hospital suddenly.

In more severe cases real nervousness and apprehension may be found, and extreme irritability be evinced, ending in active delirium.

Mania and melancholia are apt to complicate exophthalmic goitre, ~~and~~ mania being the more frequent. Both tend to end in secondary delusional insanity, especially those of persecution.

(73)

Bram believes that the nervous system is more affected after operation than other organs. He states that "post-operative changes often show a predilection for the central nervous system as evidenced by the greater prominence of the psychoses in patients operated on, than in those not operated on. In my experience, most cases of definite insanity of thyroidal aetiology are derived from this category."

In this series tremor was present in 80 per cent. of cases. The self-confidence, the incisive speech, etc. were noted in the majority of cases. Mental disorder was found in one case in this series. Case/

Case 16, and another case was seen in an asylum. Case 16 was treated for the condition medically in Leith Hospital, and later went to Canada where a partial thyroidectomy was performed. After coming home delusions of persecution set in. She was transferred from Edinburgh Royal Infirmary to Bangour Asylum, where after five months' treatment she was discharged only to be re-admitted ten months later. The prognosis in mental disorder is poor.

Another post-operative case (Case 12) showed nervous but no vascular symptoms. To generalise - more symptoms from the nervous than from the cardio-vascular system, were noted the older the patient was.

Headache is a common symptom, being present in thirty per cent. of the cases in this series. It is as a rule frontal in situation, and severe and throbbing in nature, and is therefore probably connected with the excessive vascularity.

In one case (Case 8) it had a definite periodicity - it lasted for two hours every morning, and the patient knew it would pass off at the end of that time. Her "head beat like a sledge-hammer" and she got what relief she could by putting her forehead against the cold metal bar of the mantel-piece.

Sleeplessness/



Sleeplessness seems so common a feature of the disease that it might with advantage be put among the cardinal symptoms. It was present in 60 per cent. of this series at one time or another; it seems to last several weeks or months and to disappear with improvement. In many of those showing insomnia, and in other cases also, bad dreams and nightmares were found. They seem especially prominent in those cases of nervous etiology and seemed related to the object of fear, e.g. a bakehouse girl dreamt of rats, another girl of being chased by men and by animals, another of being killed in a street accident, and yet another of "black wings flapping round her."

#### (5) The Urinary System.

Thirst is a symptom of exophthalmic goitre which though readily admitted is seldom volunteered, being to some extent overshadowed by the remarkably good appetite which is enjoyed and appreciated in this condition.

Frequency and Polyuria are occasionally met with.

Glycosuria is the chief urinary complication and is by no means rare; the tolerance to carbohydrate is definitely lowered. The quantity of sugar passed is always small; it may be present constantly or it may be wholly postprandial; in the/

the latter case it is found only on repeated examination of the urine. The glycosuria is due to hyperglycaemia.

*may be  
renal*

Schafer states that permanent glycosuria is found in 2 per cent. of cases; Garrod<sup>(74)</sup> finds that alimentary glycosuria is not uncommon and that hyperglycaemia is frequently found; whereas Blackford<sup>(3)</sup>, on the other hand, states that glycosuria is no more frequent than in any other disease.

There are several possible means of explaining this hyperglycaemia: the correct explanation is still unknown.

(1) The thyroid increases the metabolism of the whole body; it therefore increases the output of glycogen from the liver.

(2) While there is a normal amount of pancreatic hormone (insulin), compared with the thyroid secretion which is in excess, there is a relative insufficiency of insulin. And insulin is antagonistic to the withdrawal of glycogen from the liver.

(3) Excessive action of the sympathetic, whether stimulated by unknown influences or possibly by excessive adrenalism causes increased output of glycogen from the liver.

The glucose tolerance test in exophthalmic goitre is both interesting and instructive.

Todd/

(75)-

Todd and Sanford give the following as a typical example of the curves obtained in the normal person, in the diabetic person, and in the hyperthyroid person. (See Graph on p.91)

Normally the blood sugar rises to 0.15-0.16 in  $\frac{1}{2}$ -1 hour, with a gradual return to the original level by the end of the second hour.

The curve of the hyperthyroid is accentuated with more or less pronounced prolongation, whereas the diabetic curve is totally different - the blood sugar concentration is maximal only in about two hours, and does not fall to the normal level till the end of the third or fourth hour.

(76)

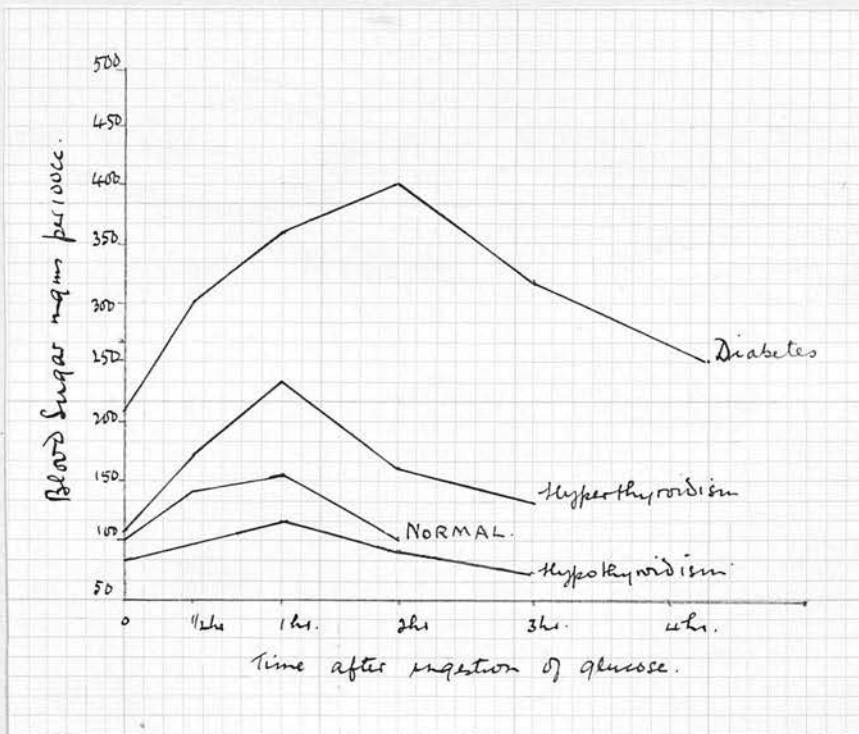
Langdon Brown believes that this curve is of importance in judging the prognosis of the case.

The association of diabetes and exophthalmic goitre is not unknown. (77) Wilder found in a series of 81 necropsies of diabetes that exophthalmic goitre was present in four of them - the diabetes in all these cases had been very intensive; one case had been mild and controlled by diet for six years, but at the onset of hyperthyroidism it became utterly impossible to control it, and acidosis and cardiac failure resulted.

Albuminuria is sometimes found. Warburton Begbie in 1863 described a very uncommon complication - intermittent albuminuria. This has since been confirmed by others, and the amount of albumin seems large/

Graph 5.Glucose Tolerance Test

after Todd and Sanford.





large.

Acetonuria while common in diabetes is only found in exophthalmic goitre in the crisis state. Its presence is other corroborative evidence in the prognosis.

In this series thirst was given as a symptom in 30 per cent. of cases, and glycosuria was present in 15 per cent. The amount of sugar passed was always small; in one case where daily observations were made, the amount of sugar passed varied from 0.06-0.25 grams per cent.

Albuminuria was not found apart from that caused by cardiac failure, neither was acetone, though the writer has seen acetone present in one fatal case in the crisis state.

The glucose tolerance test was performed in five cases (see charts). An extra curve is shown; this is from a man in whom the differential diagnosis lay between neurasthenia and early exophthalmic goitre, and the former proved to be correct. It is instructive that the blood sugar curve in his case is a normal one.

After the glucose tolerance test glycosuria was obtained in two more cases, showing that there was slight disturbance of carbohydrate metabolism.

These curves all show one thing in common - the/

*minimally*

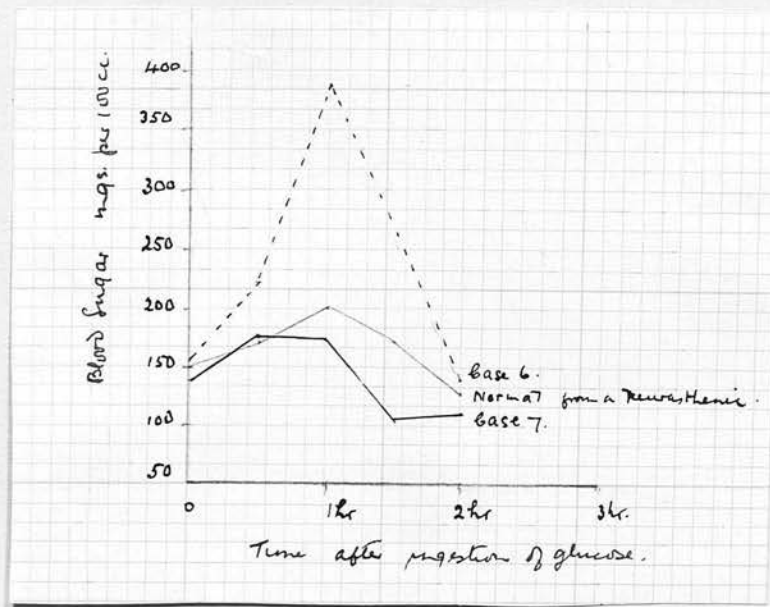
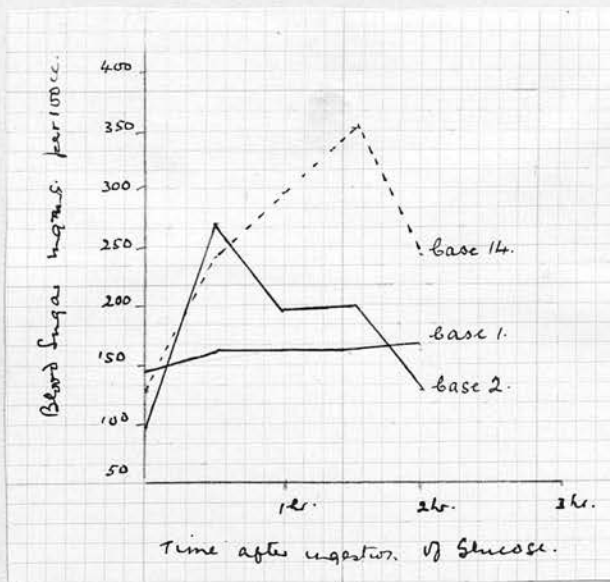
the blood sugar curve had not returned to the fasting level at the end of two hours.

All the curves with one exception also show accentuation in the height of the curve.

Appended are the results of the glucose tolerance test in the cases in this series; they are also shown graphically.

Time	Case 1	Case 2	Case 6	Case 7	Case 14	N A neurasthenic.
Fasting	.145	.098	.151	.138	.120	.140
$\frac{1}{2}$ hr.	.162	.268	.218	.185	.231	.180
1 hr.	.162	.195	.386	.179	.295	.200
$1\frac{1}{2}$ hr.	.162	.200	?	.110	.351	.180
2 hr.	.168	.139	.136	.120	.232	.130

Graph 6/

Graph 6 - The Glucose Tolerance Test.Graph 7.

(6) The Digestive System.

The most important feature in the symptomatology of exophthalmic goitre is the increased appetite when ill accompanying a loss of weight. This automatically rules out many other conditions. Nausea, vomiting and diarrhoea are also found. They may occur in the crisis state, in which they may be intractable, or they may occur in the course of the disease. Of these the most interesting is the diarrhoea. It is present in about 30 per cent. of cases, comes on absolutely suddenly and apparently without cause, and disappears without treatment. No satisfactory explanation of this symptom has been given - it is apparently a parasympathetic effect, whereas nearly all other symptoms are sympathetic in origin.

Constipation is given by some authors as a prominent feature - some believe that the disease is the result of intestinal toxæmia. The diarrhoea cannot be called a spurious diarrhoea, however.

(1)  
McCarrison has pointed out that hyp-acidity of the gastric contents is the rule in exophthalmic goitre, and this in itself is favourable to infection of the upper part of the alimentary tract. He believes that the frequency with which such/



such disorders of the tract precede the onset of the disease is becoming more frequent.

(78)

Molland Scott published a gastric analysis of fifty cases of hyperthyroidism, thirty-four of which were true Graves' disease. In this latter class there were nineteen cases of complete achlorhydria, and ten cases of hypochlorhydria. They also found in these cases that the stomach emptied very rapidly, there being very little residue in some cases at the end even of  $11\frac{1}{4}$  hours.

They believe that the achlorhydria and the hypochlorhydria can be explained in two ways: (1) associated with overaction of the vagus, causing both hastening of the gastric contents and duodenal regurgitation or (2) by direct inhibitory action of the sympathetic on hydrochloric acid secretion.

Of these the latter is the more probable.

In this series symptoms from the digestive system did not play a prominent part. The most common symptom was the good appetite, and thirst was volunteered as another symptom. The former was present in almost every case, the latter in 30 per cent. of the cases.

Constipation was not prominent, being found in 20 per cent. Diarrhoea was also present in 20 per cent. and presented the features mentioned before/

not worth  
putting without  
evidence

Why?

before. In one case (Case 8) it had an interesting periodicity - it took the place of the girl's menses, lasted 3-4 days, was intense, and began and ended abruptly.

Symptoms from the digestive tract were present only in one case (Case 5). This woman had nausea, discomfort, flatulence and constipation, and was the subject of hypochlorhydria, her total acidity being 30. This was the sole case where gastric analysis was performed.

In a few cases estimation of the fat in the faeces under a standard diet was performed. The results obtained were in each case within the normal limits.

(7) The Basal Metabolism.

The basal metabolism in exophthalmic goitre is definitely raised, though the increase is not so great as, for example, in diabetes. Exophthalmic goitre is classified by Mohler<sup>(79)</sup> and Mosenthal<sup>(80)</sup> into mild cases with basal metabolic rate of +30 to +50, into severe cases with basal metabolic rate of +50 to +75 and into very severe cases with basal metabolic rate of +75 per cent.

According to the theory of dysthyroidism this does not give a true indication of the disease. For the disease is held to vary with the ratio of normal and abnormal thyroid products, and whereas a case with a basal metabolic rate of normal may have a nervous phenomena + + + , another case may have no nervous phenomena and a basal metabolic rate of + + + , and whereas iodine has a definite and marked effect on the former case, it has not so on the latter.

Operation on the thyroid gland results in nearly all cases in a reduction of the basal metabolic rate at least temporarily to about normal. This shows that the part played by the thyroid on the basal metabolic rate cannot be belittled, even though there may be dissension on whether normal or abnormal thyroid products cause this increased metabolism.

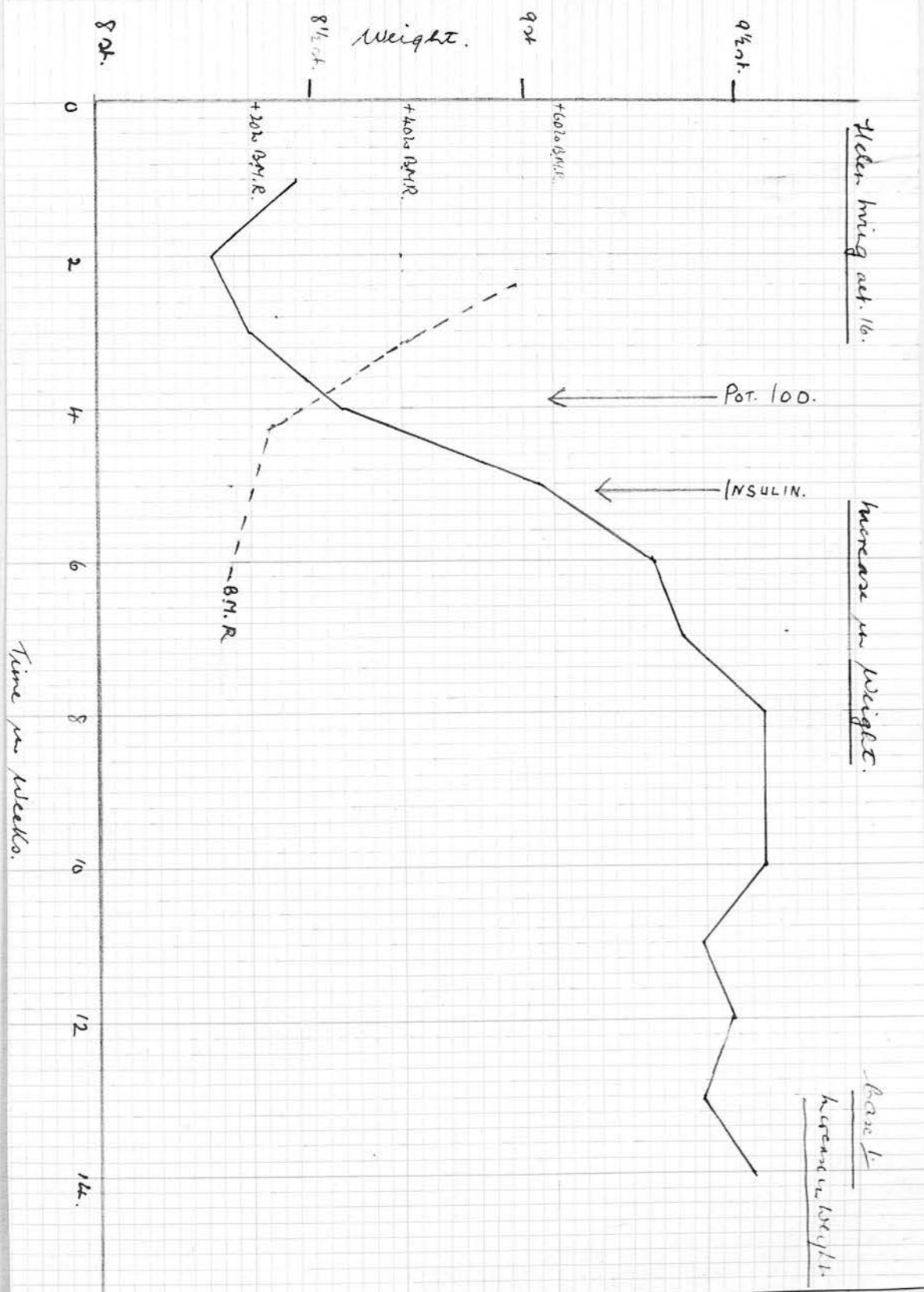
This increased basal metabolism affects all the/

Bad  
not so

not clear





Graph 8.- Case 1, Increase in Weight.

(8) The Blood.

In this series the blood picture was not studied in detail, though several cases showed a lymphocytosis and a secondary anaemia.

The blood picture is given in detail under Pathology.

(9) Vasomotor and Trophic Symptoms.

The most common symptom is a sensation of warmth and a tendency to flushing of the skin. The skin is fine and warm and moist, rather translucent, soft and satiny. There may be an erythema localised to the gland, or found on the face, neck and upper part of chest, or uncommonly found all over the body. Dermatographia may also be found.

Perspiration may be excessive especially of the hands and feet and armpits, and pigmentation is a common feature especially in more elderly cases. The face, especially below the eyes, and the axilla and groins are the usual sites. Such pigmentation is in the writer's experience most marked in those cases showing cardio-vascular degeneration. The pigmentation may be so bad as to suggest Addison's disease; Barr believes that hypo-adrenalism is the cause of the pigmentation, while Etienne<sup>(81)</sup> has described/

described a series of cases of Graves' disease showing pigmentation, which he believes due to the action of the sympathetic in producing a disturbance of pigment production and a disturbance in the distribution of the melanin.

Vitiligo and leucoderma may also occur on the neck and extremities; two cases in this series had leucoderma of the neck and chest.

The hair is scanty on the body, and that of the head tends to be brittle, turn grey soon, and to fall out.

Pruritus is described, occasionally very severe and without any pathological basis. This symptom was not found in this series.

Perhaps the most common of the trophic symptoms, however, is the change in the nails. According to Plummer the nails become brittle and show longitudinal striation. If the condition becomes more marked the upper surface of the nail becomes slightly concave with slight elevation of the distal end, after the form of a scoop. This results in an irregular separation of the soft cutaneous structures beneath the nail from the nail itself, and in this space dirt collects, thus resulting in the symptom of "difficulty in keeping the nails clean."

Brittle nails and difficulty in keeping them clean/

clean were symptoms present in about 15 per cent. of the cases. Two sisters in Haddington (Cases 8 and 9), however, gave almost the above description in its entirety. They said that their nails were brittle with lines on them, and that the nail was separated from its bed and that dirt got in, and resulted in great difficulty in keeping them clean. One sister (Case 8) who was a very bad case, went further - she said that when she was very ill this separation took place to about half way down the nail, as she got better the separation grew less, thus a very minor point in prognosis, noticed by the patient herself.

Loss of subcutaneous fat, delicate bones and laxity of the ligaments, especially of the hips, occur. Eason has also pointed out a common feature in the disease - an increase of the "carrying angle" at the elbow. This was fairly common in the cases in this series, both male and female, but was not constant.

#### (10) The Respiratory System.

The breathing is usually described as increased in rate, superficial and irregular, with diminished amplitude in the excursion of the chest.

(11) /



(11) The Reproductive System.

Loss of sexual power in the male has been described - it is not common.

In women menorrhagia is described as the most common condition. In the writer's series only two cases had a history of menorrhagia, whereas 40 per cent. gave a history of amenorrhoea. While menorrhagia is apt to be followed by amenorrhoea from anaemia and emaciation, previous menorrhagia was not admitted in these cases. Dysmenorrhoea is also described, but it is probably not a characteristic feature of the condition. h20

On the outlook with regard to pregnancy there is no unanimity of opinion. The majority of people believe that it has an unfavourable influence. Some women seem to improve during <sup>(82)</sup> destation, but the bad cases die. Anspach states that patients with Graves' disease are usually sterile and that pregnancy exercises a decidedly unfavourable impression on the prognosis.

The mammary glands do not seem to share in the general loss of subcutaneous fat. wrong

Amenorrhoea was common in this series. In several cases it was of short duration, but one girl had 6 months, another 18 months, and a third at the age of 39 had 6 years of amenorrhoea.

(12) /

(12) Less Widely Known Symptoms.

Other and less widely known symptoms are:

(1) Weakness. (83)

Murray has called attention to the persistent sense of fatigue as one of the earliest symptoms. This is a common symptom in many illnesses, was frequently given here, and was described as "weakness", "run down", "always tired", etc.

(2) Weakness of the quadriceps muscle has been described by Blackford, Plummer and other American authors. It is described by the patients as a giving way at the knees, or as a weakness in climbing the stairs. One case in this series gave this symptom. It can be explained by the atrophy of muscle and the deposition of fat which occurs in its place.

(3) The voice, according to Horder (65) is rather high in pitch and becomes weak. This was very pronounced in Case 25.

(4) Epistaxis has also been described.

(5) One symptom given by two patients (Cases 3 and 8) in this series was that they felt the ground was rising up to meet them and then falling and then rising again. Both had occasionally fallen because of this, and one patient (Case 3) found it her most troublesome symptom. The writer is unable/

unable to offer a correct physiological explanation.

(6) Another symptom is that these people do not tolerate hot weather well - they perspire too much. They exhibit great tolerance to cold - they wear lighter garments and use fewer bed clothes; this is probably a sequence of the vasomotor changes.

v. /

## V. Differential Diagnosis

In a fully developed case the diagnosis of exophthalmic goitre is comparatively simple, but there can be few more difficult problems than the early diagnosis of exophthalmic goitre.

Diagnosis is rendered difficult by the fact that exophthalmic goitre shows signs and symptoms similar to those found in a normal person under strain, whether physical or mental. Added to this difficulty is the fact that in early exophthalmic goitre there is often no localising sign or symptom e.g. pain in the gland itself. Moreover the anxiety and self consciousness which may be produced in a highly strung patient may result in restlessness, tachycardia and palpitation and even tremor, all cardinal features of the disease.

One would therefore look to laboratory tests for help: several are available.

### Laboratory Tests

Of these the most satisfactory is the Estimation of the Basal Metabolic Rate. As Earle and Goodall<sup>(84)</sup> point out, this method had not been feasible for clinical diagnosis until a simple apparatus<sup>(85)</sup> was put forward by Benedict. By basal metabolism is meant the amount of oxidation taking place in the body in the post-absorptive condition - i.e. after twelve hours' fast and at complete rest. It is measured by the amount of CO<sub>2</sub> produced from the oxygen inhaled /



inhaled , or by the heat produced. M'Caskey says "it places before the clinician, with very moderate effort, an exact measurement of the speed with which the stream of life's chemism is being driven." It is, therefore, possible to follow the course of the disease on a chart by making repeated readings.

But is the very apparatus itself not enough to produce temporary increased metabolism in a normal patient, and much more so, therefore, in an apprehensive sufferer from exophthalmic goitre ? It cannot be too strongly emphasised that one reading can be considered of no practical value. Several readings must be made to accustom the patient to the apparatus before making the initial reading, and a reading of less than  $+15\%$  should not be considered abnormal. <sup>(81)</sup> Crile has pointed out that the rate gives no information about the reserve in the liver, the central nervous system or the myocardium, and Professor Cathcart emphasises the need of caution in interpreting the findings. The Basal Metabolic Rate is increased in fevers, anaemia and leukemia, Diabetes Mellitus , Cardiac Dyspnea, and Asthma and Pituitary Disorders. It would seem to be of most value in differentiating exophthalmic goitre from Tuberculosis or from Neurasthenia.

The amount of disturbance produced by the estimation of the basal metabolism of a patient is well seen in the Pulse chart of Case 1.

Goetsch's Test.

(89)

Goetsch claims that the sympathetic nervous system is sensitised to the action of epinephrin in the presence of excessive thyroid secretion. He injects 0.5cc of 1/1000 adrenalin which he says produces no effect in a normal person. He claims a positive result in the increase in pulse rate or blood pressure of more than ten points, and in an increase in those signs and symptoms from which the patient suffers - nervousness, throbbing, tremor and vasomotor disturbances. In  $1\frac{1}{2}$  hours the patient has returned to her previous state.

This test does not find universal acceptance. Peabody and others have found the reaction in normal people, while Harrower believes it to be especially helpful in establishing a diagnosis in latent cases. According to Crile it is positive in 85 per cent of cases.

Loewi's Mydriasis Test.

This was originally introduced as a test for pancreatic disease. If a drop of 1/1000 adrenalin is instilled into the conjunctival sac and another five minutes later, the pupil will dilate within  $\frac{1}{2}$  hour if the pancreas is inadequate. The test is based on the antagonism between the pancreas and adrenals which normally balance one another. It was found that excess of thyroid secretion by sensitizing the sympathetic nerve endings to adrenalin caused /

caused this reaction to occur in the absence of any pancreatic defect. This test is of some value in the diagnosis of hyperthyroidism.

#### Glucose Tolerance Test.

It has long been known that sugar tolerance is lowered in hyperthyroidism - the study of the curve of sugar in the blood after a dose of 50 gms. of dextrose is the usual test and is very delicate. In the normal individual this will produce a rise in blood sugar to about 0.14% which quickly subsides in about one hour. In hyperthyroidism the rise is greater and more prolonged while actual glycosuria may occur. This test is one of considerable importance. (see Chart)

#### Thyroid Function Test.

This, as Harrower says, is obviously not a measure to be used in frank hyperthyroidism. On the first day  $\frac{1}{2}$  gr. of thyroid extract is given, on second day 1 gr. , on the third 2 gr. at 8, 10, 12 and 2 o'clock. The pulse is better at 9, 12, 3, 6, and 9, for one day preceding the test and for the next five days.

If the thyroid is irritable, the pulse will show an early rise and will continue to be rapid for two or more days after the test, while a normal thyroid will only show a slight fleeting rise. There is no doubt as to the efficacy of the test, but /

*Refers*

but its advisability is much more questionable.

#### Quinine Hydrobromide Test.

Bram of Philadelphia made use of the fact that hyperthyroid patients are more tolerant of quinine than normal patients. Whereas cinchonism occurs in normal people after the ingestion of 30 - 50 grs., subjects with hyperthyroidism can continue taking this dose for weeks or months without toxic effect, and with benefit to the symptoms of the disease.

Several clinical features are of definite value in diagnosis -

- (1) prolonged vibrating bruits with maximum intensity at the superior poles of the thyroid.
- (2) increased pulse pressure accompanying a tachycardia.
- (3) increased appetite when ill along with loss of weight.
- (4) increased tolerance for cold along with decreased tolerance for heat.
- (5) thirst accompanied by glycosuria in an enlargement of the thyroid.

#### (1) The Neurosis    Anxiety Neurosis.

Stoddart regards exophthalmic goitre as a neurosis, and has classified it as a special variety of the anxiety neurosis. He states that the symptoms are the same, except for the exophthalmos & the goitre /



goitre, which are additional in exophthalmic goitre.

- Two points of difference present themselves -
- (a) increased appetite and increased tolerance for cold, so common in exophthalmic goitre, are not found in the anxiety neurosis, except very rarely and then only at its beginning.
  - (b) there seems to be a subtle difference in the mental state. In exophthalmic goitre there is admittedly anxiety and apprehension, but coupled with this is often an amazing degree of self assurance and fearlessness, e.g. to operation. This may sound paradoxical, but it seems to exist.

Still the two important points in the differential diagnosis are admittedly the exophthalmos and the goitre.

## (2) The Psycho-neurosis - Neurasthenia.

Osler states that early exophthalmic goitre may resemble neurasthenia, and both diseases do occur at the same period of life.

In both diseases there may be tremors, emotional instability, restlessness, insomnia, nausea, and vomiting and diarrhoea, loss of weight and polyuria.

The emotional tone of neurasthenia, however, is one of depression - dull, languid speech and poor capacity for work: the patient is anxious to work but the least exertion, either mental or physical, results /

results in immediate sense of fatigue. In Exophthalmic goitre the picture stands in marked contrast, - the patient is usually animated in appearance, incisive in speech, and almost gluttonous in her capacity for work. Increase in appetite is rare in neurasthenia, common in exophthalmic goitre.

The moist sallow skin and cold extremities of the neurasthenic are in marked contrast to the moist hyperaemic skin of the exophthalmic: the neurasthenic is particularly sensitive to cold, and is usually overclad, the opposite holds good in exophthalmic goitre. The tremors of the neurasthenic are coarser and less rapid; tachycardia is uncommon - after rest the pulse is usually a slow one -, and the systolic Blood Pressure and the pulse pressure are never increased: goitre and eye signs are absent. Hamilton and Lahey<sup>(91)</sup> emphasise the sharpness of onset of exophthalmic goitre, and the vague onset of neurasthenia. Fussell<sup>(92)</sup> gives the following points for differentiation - in neurasthenia there is usually loss of appetite, no increase in Basal Metabolic Rate, no reaction to thyroid feeding, and the Goetsch test and the sugar tolerance are normal.

### (3) Hysteria.

This differential diagnosis is necessary in cases where hysterical tremor and tachycardia co-exist: it is one of extreme difficulty, especially so /

so when it follows shock, and is associated with apprehension. The mental state in hysteria is peculiar: patients are apt to laugh and cry in the wrong place: the tremors rarely resemble exophthalmic goitre - they usually take the form of rhythmical spasms and different parts of the body are involved in different cases. There is no increase in Basal Metabolic Rate, and an increased blood pressure and other minor points are lacking.

#### (4) Toxic Adenoma.

Unless an adenoma is definitely palpable in the thyroid, and it may not be, if situated as it is in rare cases, behind the clavicles, the differential diagnosis is one of extreme difficulty.

Toxic adenoma usually occurs later in life than exophthalmic goitre, 78 per cent being over 40 years of age, and the disease being rare before 30 - in exophthalmic goitre 60 per cent occur before the age of 40.

In both diseases there are present from increased metabolism, sweating, excessive warmth, tachycardia and palpitation, increased pulse pressure, and nervousness, loss of weight, loss of strength, and ultimately auricular fibrillation and cardiac failure. Though in both diseases there is present a subjective restlessness and even tremor from the increased metabolism, in toxic adenoma there is not present that peculiar objective restlessness of exophthalmic goitre - the appearance of the patient is /



is rather just an expression of more than normal stimulation.

Again, the stare, the exophthalmos and the tendency to gastro intestinal crises are practically unknown in toxic adenoma. The thyroid is less vascular and a definite adenoma can usually be felt. The characteristic bruits over the superior poles of exophthalmic goitre of the gland which W. A. Plummer believes to be next in importance to the ocular signs in the diagnosis are absent. Lastly the Basal Metabolic Rate in adenomatous goitre is not so high but persists at a more definite level; in exophthalmic goitre it shows wider fluctuations caused by exacerbation and remission.

#### (5) Simple Goitre.

There is no definite line of demarcation between simple and exophthalmic goitre. Only a detailed examination of the patient, especially with regard to thyroid, eye signs, and cardiac changes, can help to differentiate, and much help can be gained by estimations of the Basal Metabolic Rate. The diagnosis is of special difficulty in women with large colloid goitres accompanied by nervousness from medical examination.

#### (6) Antonomic Imbalance.

This differential diagnosis is almost impossible. The sole definite difference in the literature /



(93)

literature consulted is that of Kessel & Hyman who state that "there is never present in autonomic imbalance a distinct <sup>and</sup> continuous elevation of basal metabolism. This serves as the crucial differential point from Graves' Syndrome." Both diseases run a prolonged course, and both show pathological changes in the involuntary nervous system. Both may show in their etiology focal infection, psychic trauma, and sex epochs. The symptoms are strikingly similar, and in autonomic imbalance hyperplasia of the gland is often present - probably a secondary phenomenon. Local manifestations in a single organ e.g. stomach or heart, are more common than in exophthalmic goitre; they may attract attention to the organ itself and the total diagnosis be missed.

#### (7) Diabetes Mellitus

The differential diagnosis is not difficult. In both diseases there is increased appetite, increase thirst, loss of weight, and there may be glycosuria and polyuria. These symptoms are never so marked in exophthalmic goitre, and the amount of sugar passed is always small; acetone is only found in the crisis state. Though hyperglycaemia is present in both diseases, a glucose tolerance test is conclusive. (see Chart)

#### (8) Tuberculosis

In early tuberculosis there may be no physical signs and only weakness and tachycardia as symptoms.

The /

The addition of loss of weight, sweating, and possibly diarrhoea in the gracile type of person, makes one think of tuberculosis. Blackford points out that in a series of eighty-six post mortems on exophthalmic goitre no active tuberculosis lesion was found, though twelve healed scars were present. He thinks that the two diseases rarely co-exist. Examination of chest and sputum, and estimation of the Basal Metabolic Rate are the important factors in differentiation: Goetsch claims that his test is useful in this instance.

(9) The Symptoms of the Menopause.

Tachycardia, and palpitation, and nervousness, and flushings are common to both diseases. Exophthalmic goitre does not usually develop after forty, however, and an examination of the eyes and thyroid, and Basal Metabolic Rate estimation are usually sufficient to exclude exophthalmic goitre.

(10) The Irritable Heart of Soldiers.  
(Neuro-circulatory Asthenia)

While there is no goitre, and no ocular signs are found, the symptoms are much the same, dizziness and palpitation, throbbing vessels, perspiration and faintness. Fussell<sup>(92)</sup> finds no reaction to thyroid feeding, no increase in Basal Metabolic Rate, and while Goetsch's test is +<sup>ve</sup> in 60 per cent of cases, sugar tolerance is rarely affected.

Two lesser differential diagnosis present themselves.

(11) Paroxysmal Tachycardia.

Where nervousness and anxiety and an increased pulse rate are found, the tachycardia comes and goes with equal suddenness and the patient is quite well between the attacks.

(12) Pregnancy.

Exophthalmic Goitre and amenorrhoea along with the vomiting of crisis might be confused with pregnancy.

### PROGNOSIS

A guarded prognosis must always be given at first in each case. The duration course, and ultimate end of the disease in any individual must be uncertain. Remission must not be looked upon too favourably - it is too frequently a temporary phenomenon which is followed later by an exacerbation. Even after apparent subsidence of the disease relapse may occur.

Acute cases may end fatally in a few days or in a few weeks, may terminate in speedy recovery, or, more frequently, may become chronic. Chronic cases may run a slow course extending over many years with exacerbations alternating with remissions, they may develop an acute exacerbation with possible fatal end, or they may clear up. There would seem to be a definite tendency to spontaneous cure in the disease.

In a few cases almost wholly confined to those which begin acutely and end in speedy recovery, it would seem probable that exophthalmic goitre is a functional disease: that functional involution of the gland occurs and no permanent pathological changes are left in it. Where spontaneous recovery, or even a condition of submyxoedema or myxoedema, is found in the more chronic cases, this would seem to be due to involution atrophy of the hypertrophied epithelium, /



epithelium, the atrophy being either primary or secondary to fibrotic changes.

Even when recovery does take place, the disease does not leave the patient in the same condition as before the attack - usually some traces remain e.g. irritable heart, vasomotor neurosis, goitre, muscular weakness, or cardio-vascular degenerations. Trousseau remarked that when recovery took place, the swelling<sup>and</sup> induration of the thyroid,<sup>and</sup> the prominence of the eyes always remained. (94)  
Ord & MacKenzie seem to differ, and say that the exophthalmos sometimes completely disappears, and that the goitre may vanish in mild cases. The writer has seen the goitre disappear, but he has never seen total abolition of the exophthalmos.

(3)  
Plummer has shown that in an average of 9 months from the onset there is an explosion of symptoms that prostrates the patient for a time. If the patient does not die, improvement sets in and continues with ups and downs till an average of two years from the onset when there is a second crisis. The second crisis is not so severe as the first - the patients rarely die but the cardiac condition is worse.

The condition goes on with ups and downs for three - eight or ten years, when gradually the hyperplasia of the thyroid and the symptoms are played out. The end result may be complete recovery, but only /

only too often it is a patient without active intoxication but a wreck from chronic cardio renal and hepatic degenerations.

Schafer states that the general toxic symptoms usually reach their maximum in twelve months, after which there may be a return to normal, or they may persist with fluctuations for two - four years.

(95)  
Marion Read believes that acute cases with well defined onset do better than the chronic insidious type, and that males are more resistant than females. The writer's experience serves to confirm this opinion.

Pregnancy according to Anspach exercises a decidedly unfavourable influence on the prognosis. Horder believes that these patients go through acute intercurrent illness e.g. influenza and pneumonia surprisingly well. This is quite opposite to the general consensus of opinion, which is, that hyperthyroid cases exhibit a definite lowered resistance to acute infection, whether generalised or localised. Eason in pointing out that infection may lead to a fatal end in hyperthyroidism, suggests a comparison with the deterioration that occurs in diabetes mellitus under similar circumstances. One case in this series - Case 24 - had an infected bursa on his elbow, it was extremely resistant to treatment and ultimately caused caries of the bone underneath. /

underneath. The presence of glycosuria renders the prognosis a little worse.

The prognosis respecting both recovery and expectation of life is rather more grave when episodic mental disorder e.g. mania and melancholia supervenes of forty-three such cases collected by Kirschel only six recovered from their mental disorder.

About 10% die directly as the result of the disease, either from (1) heart failure, which may be sudden or may follow loss of compensation, or from (2) general weakness and exhaustion from intractable vomiting or diarrhoea or mania. Others die from pneumonia and a few from tuberculosis .

Buschan out of nine hundred cases found fatal result in 105. In the opinion of Ord & MacKenzie in well marked cases of the disease, 25 per cent die from it, while in 50 per cent more or less complete recovery takes place.

(96)  
Hale White has pointed out that in exophthalmic goitre the death rate is double that of the normal population, being 15 per cent for those treated medically in his series, and being  $7\frac{1}{2}$  per cent calculated for similar people at the same ages.

Cohen thinks that at least 70 per cent recover either spontaneously or under non-surgical treatment. He holds that Hale White is correct in his opinion that most patients are as likely to perform their ordinary /



ordinary duties without operation as with operation.

The prognosis with surgical treatment is discussed under that heading. To avoid controversy here, it is sufficient to state that immediate marked improvement often follows partial thyroidectomy, which operation is associated with a definite mortality.

Unfavourable signs in the prognosis are progressive emaciation, loss of strength, uncontrollable tachycardia, diarrhoea, dyspnoea and violent tremors. Acute exacerbation must always be looked upon with alarm, it commonly follows influenza or operation and is characterised by dilated heart, rapid irregular pulse, delirium, collapse, oedema, fever, dyspnoea, anuria, coma and then death.

Auricular fibrillation is common in the later stages of exophthalmic goitre. As stated before even in its presence the cardiac function may be surprisingly good and may seem hardly to incapacitate the patient. One man in this series - Case 23 - had been working as a joiner for years with permanent auricular fibrillation. It is a notable feature that digitalis does not seem to have much effect on this already slow fibrillation.

The guides to improvement are (1) gain in weight, (2) slowing of pulse, (3) decrease in pulse pressure, (4) fall in Basal Metabolic Rate, (5) lessened nervousness, (6) increase in strength, and (7) /



(7) ability to sleep.

It would appear that the prognosis of exophthalmic goitre varies with each individual case. As a general rule the more acute the case the greater is the danger to life: on the other hand those cases which have a definite onset have a better prognosis than those which come on insidiously. The prognosis is better in women than in men.

Etiology also plays a part in the prognosis. The nature of the exciting factor, its duration and the possibility of its complete elimination, are fundamental items. Lastly there is the most potent factor in both prognosis and treatment - rest, both physical and mental. Rest is the sheer anchor of treatment, and its possibility, too often, unfortunately, linked with the economic position of the patient, is a basic factor in prognosis.

VI - TREATMENT.

(VI) Treatment.

As is usual in a disease so obscure in its pathology, so chronic in its course, and so variable in the severity and combination of its many symptoms, innumerable methods of treatment have been advocated.

'Specific' results have been claimed for general medical treatment, for tonsillectomy, for X-rays to the thyroid or thymus or both, for mechano therapy and spondylo therapy, for endocrine therapy and for surgery - from injections to ligations and from partial to total thyroidectomy.

(98)  
Crile states that in the literature the cure of hyperthyroidism has been credited to each of 239 drugs and other methods of treatment (the figures are those of Marine).

This would lead one to believe that a non-specific factor exists. It may be one of two things - either physiological rest or the tendency to spontaneous cure.

Before entering into a detailed description of the more important methods of treatment, it is obviously outside the scope of any thesis to discuss all of them, it is wise to consider the natural course of the disease. Knowledge of this is very imperfect; hospital records deal only with severe cases/

cases, and social position enters largely into the possibility of adequate management of the disease.  
(99)

Baker has stated that the course of primary exophthalmic goitre "is probably two to three years, no matter how you treat it (medically, surgically or radiologically". He does, however, qualify this statement by saying that relapses do occur. (100) Kessel, Lieb and Hyman studied 50 cases and maintained that sufficient recovery to enable a resumption of work resulted from rest and symptomatic treatment only, without surgical or X-ray intervention. (101) Read published curves to show that as measured by the basal metabolic rate the progress is much the same, whether general, medical measures, X-rays or surgery are employed. (102) Holmes, Means, Porter, Richardson and Star, while confirming this in general, believe that partial thyroidectomy has a definite effect on the course of the disease.

It is therefore already obvious that the treatment of exophthalmic goitre is in a state of chaos. It is equally obvious that each specialist will dogmatically boom his own speciality; it is still more obvious that the literature must be read dispassionately.

The tendency to spontaneous cure is so definite an entity that there is ample justification for/



for conservative treatment in the first instance. Even the most perfervid supporters of surgical treatment do not believe in operating within six months of the onset of the disease. It is in the first six months that the physician's opportunity lies, and in this time he can do much, not by empiricism and grape-shot methods, but by treating his patients on the broader lines of physiology, and on the information gained by careful clinical examination and the determination of the exciting aetiological factors in each case.

### Medical Treatment

#### General Measures.

##### Rest.

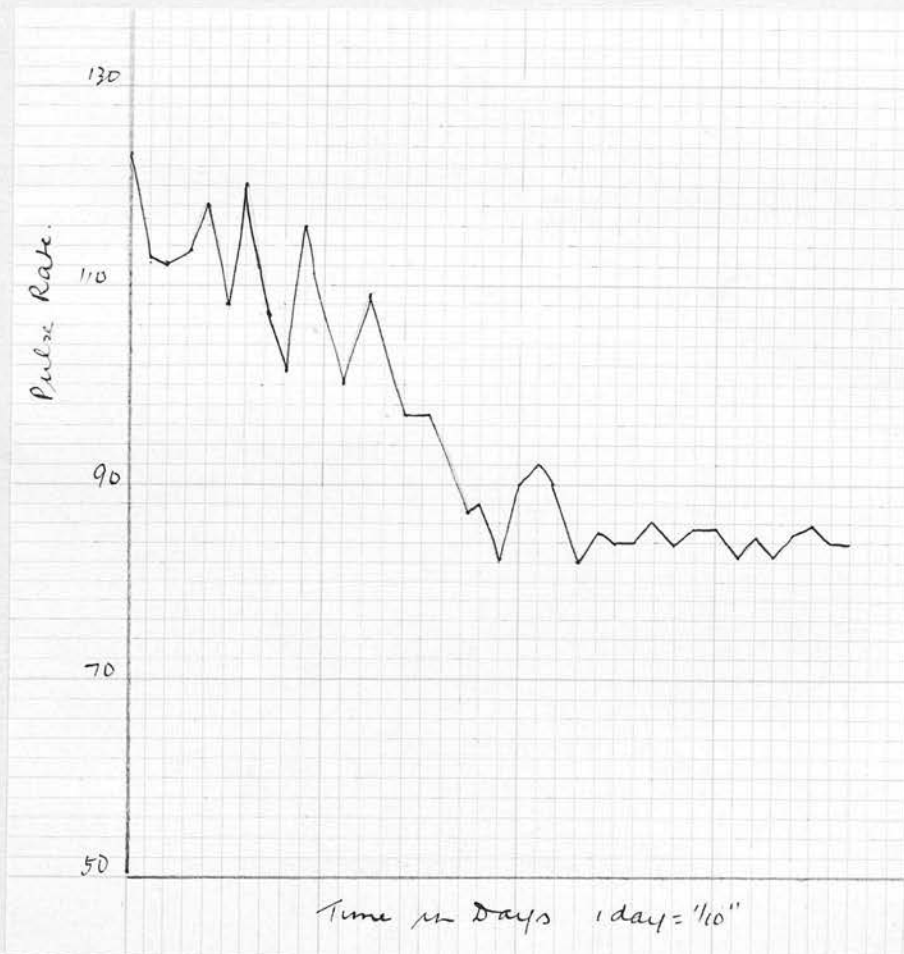
Of all the methods of treatment rest is the most important. It is indicated by the tachycardia, the muscular weakness, and the nervous irritability. Physical rest is not more important than mental rest. Unfortunately there is probably no disease where these are so difficult to obtain - the patients are consumed with a desire to do something, they are often slightly wilful and headstrong, and in so many cases the opportunities for rest are unhappily linked with the economic position of the patient. It is therefore wise to gain the patient's confidence and/

and talk over any anxiety or other psychical factors  
and  
discovered in his aetiology/when possible to  
eliminate them.

For the first few weeks the patients should  
be wholly confined to bed; after that time has  
elapsed, each case must be judged on its own merits.  
The effect of complete rest in bed is seen in the  
accompanying chart (Case 16).

Graph 9.

Case 16 - Action of Rest on Pulse.



In the most severe cases rest up to Weir Mitchell treatment is indicated; in cases of lesser severity long hours for sleep, rest in the middle of the day, and the avoidance of excessive physical and mental effort are sufficient.

Nervousness and inability to sleep should be treated without drugs if possible. These patients are intolerant of heat, so there should be plenty of fresh air in the bedroom and the bed clothes should be light. Hot milk or cocoa may be given or drowsy feeling may be induced by the taking of a bath at a little above body heat a quarter of an hour before retiring. Bromides are the stand-by - given as such or as sedobrol. Some claim that belladonna has a sedative effect on the nervous system, the patient feeling less excitable and nervous; whether it exercises its anti-sudorific action in this condition is very doubtful. Stronger hypnotics should not be given unless mental symptoms, e.g. mania, supervene.

#### Elimination of Sepsis.

If sepsis is adequately dealt with, the disease runs at a lower level. The two most common foci of sepsis are the teeth and tonsils, both easily eradicated.

On the theory of intestinal toxæmia the  
bowels/

bowels must be dealt with either medicinally or dietetically. Laxatives or daily enemas may be employed, and intestinal antiseptics, e.g. kaolin or  $\beta$ -naphthol or salol may be tried. Sodium phosphate probably owes its reputation in this disease to its laxative effect, and not to its action on the medulla which Trachewsky mentions.

### Diet.

At present there is no clear indication of the value of any special diet. Chalmers Watson has shown that a meat diet produces changes in the thyroid gland in animals suggestive of hyperthyroidism. (28) McCarrison claims that excess of fats in the diet may produce a relative iodine deficiency and suggests that fats should therefore be reduced. (29) Professor and Mrs Mellanby in their work on experimental rickets have shown that increase of butter in the diet of puppies caused a fivefold enlargement of the thyroid gland, and that cod liver oil does not produce this change. They also found that in Graves' disease the addition of butter intensified the tachycardia and nervousness and was followed by loss of weight. Further investigations are obviously necessary before any conclusions can be made; it does not follow that a diet which will produce/



produce changes in the thyroid gland of healthy animals will produce similar effects in the thyroids of human sufferers from Graves' disease.

A liberal nutritious diet is obviously desired in patients whose metabolism is increased. To increase the weight is to better the prognosis. Happily the patients are often hungry, and only in those few cases with capricious tastes need injunctions be made. At present an ordinary diet arranged to suit the habits and status of the patient is all that is indicated.

#### Tachycardia.

Rest in bed is the sheet anchor in the treatment of tachycardia. The use of "cardiac tonics" is to be avoided unless and until symptoms of cardiac failure ensue, when digitalis or strophanthus or strychnine may be given. In the opinion of Harris <sup>(70)</sup> digitalis is contra-indicated owing to the systolic blood pressure being already raised; in my experience nothing but good has been afforded by its use. An icebag or Leiter's coils may be applied over the praecordia; their action is questionable. The tachycardia can be reduced by the administration of iodine, q.v.

Drug/

Drug Treatment.Iodine.

The action of iodine in exophthalmic goitre ranks as one of the most important discoveries in the progress of medical science of this century.

(103, 104)

Marine had stated that iodine given in any form and by any route was quickly bound up by the thyroid gland. Its use in hyperthyroidism was universally vetoed, chiefly because Kocher (105) had pointed out that patients with endemic goitre were prone to develop hyperthyroidism if treated with iodine. Some idea of the confusion still prevalent is shown by the following statement from Boyd's Surgical Pathology, pp. 241 and 243.

"Iodine in food exists in a combined organic form, which cannot be utilised until it is split up and converted into sodium iodide, and presented as such to the thyroid. There is no advantage, therefore, in giving iodine in any form other than sodium iodide." Later he states "In considering the effect of iodine administration in exophthalmic goitre a distinction must be drawn between iodine and sodium iodide. The use of sodium iodide is more likely to do harm than good, for it merely adds fuel to the already blazing fire. Iodine in the form of Lugol's solution, on the other hand, may have exactly the opposite effect, particularly on the basal metabolism; its use may be from the/

the intestinal antiseptic action of iodine, whereby stimulating influences are removed. Marine and (106) (107) Lenhart, however, and later Neisser, treated Graves' disease with small doses of potassium iodide with encouraging results, and in 1921 (108) Loewi and Zondek confirmed these observations. Its use in exophthalmic goitre was crystallised by Plummer, who offered a hypothesis as to its (109) action, and along with Boothby published a report on 600 cases.

Plummer suggested that certain clinical findings of exophthalmic goitre - the ocular findings, the nervous phenomena and the tendency to crisis - were due to a perverted secretion; he further suggested that this perverted secretion was an incompletely iodised molecule, and sought to explain the clinical improvement which he found after the administration of iodine to the possibility that iodine might lead to more complete iodisation of thyroxine in the gland.

While this hypothesis is not yet proved, it certainly warrants serious consideration; on the other hand there can be no doubt that iodine has gained for itself a definite place in the treatment of exophthalmic goitre. To what extent it can be used still remains to be seen; that it has a definite/

definite therapeutic value is abundantly shown, histologically, chemically and clinically.

Histologically.

(110)  
Reinhoff examined the histological changes in the thyroid gland after the administration of Lugol's solution, and found that the typical histological picture of exophthalmic goitre had been changed to that of a resting colloid state. He concluded that artificial remission of the disease had been produced by the iodine.

(111)  
Jackson also pointed out this histological change, and it was later confirmed by  
(112)  
Wilson. Wilson showed that the parenchymal cells are no longer columnar and hypertrophic, but are cuboidal, flattened, or even markedly atrophic, and that the follicles are filled with lightly staining colloid of apparently recent deposition.

He further showed that such flattened atrophic cells may be found in the follicles of thyroids of patients with exophthalmic goitre who have histories of exacerbations and remissions; in his judgment the histological picture of remission and that of iodine treatment were strikingly similar.

Chemically.

In the normal desiccated thyroid gland the amount of iodine present in the form of thyroxine is/



is approximately 50 per cent. of the total iodine.  
(113)

Weir has shown that in exophthalmic goitre the total amount of iodine present is less than normal, and the percentage of the total which is in the form of thyroxine is definitely reduced. After the administration of Lugol's solution, the total amount of iodine present in the goitre rises, and the percentage in the form of thyroxine increases. Clinically.

Plummer claims that clinical results can be observed in two hours with the maximum result in seven days; he finds that the vomiting of crisis can be stopped in 48 hours, and that a person in coma will become rational in a few hours. He enumerates his results as follows:

1. The disappearance of the stare.
2. The disappearance of the characteristic nervous phenomena including the crisis and crisis deaths.
3. Cessation of the development of exophthalmos and in some cases rapid regression.
4. Reduction of the entire physiological status to that of hyperfunctioning adenoma of the thyroid.
5. Marked reduction of the operative and non-operative mortality.

He finishes his paper by stating that "how far the trial of iodine administration and avoidance of stresses and other symptomatic medication under critical/

critical control should be pursued early in the history of the disease before resorting to surgical measures is an open question."

(111)

In the opinion of Jackson clinical improvement becomes evident on the second or third day with abatement of the nervous, vascular and digestive symptoms. The anxiety and insomnia vanish, and the pulse becomes slower. The necessity for preliminary ligation of arteries is eliminated and the operative death rate is reduced. Iodine will not permanently cure but merely temporarily alleviate the symptoms of exophthalmic goitre.

(114)

Dunhill states that after iodine administration there is a definite fall in the pulse rate and in the basal metabolic rate, the excitability of the patient is decreased, the gland is rendered less vascular, and the operative mortality is reduced from 4 to 1 per cent. In his experience the clinical improvement is maximal in about seven days, and he believes that no useful purpose can be served by continuous administration.

(115)

Cole summarises his experiences in 10 cases of true exophthalmic goitre treated by iodine by stating that the symptoms and signs are lessened; a point of maximal improvement is reached after from 2-6 weeks of continuous treatment and most cases then relapse slowly even though iodine is continued. A state of low hyperthyroidism persists. The weight is increased and the basal metabolic/

metabolic rate decreased.

Indications for smaller dosage are in his opinion, an increase in symptoms, a hardening of the gland, severe nervous symptoms or loss of weight.

(116)  
Walton states that the results of iodine therapy are often remarkable; the pulse after a day or two falls from 120 to 80, the patient becomes much calmer, the nervous tremor and excitement may almost entirely disappear. Sleep is regained, the weight increases, and intestinal upsets may disappear. These results, however, are only temporary, and he agrees with Fraser that if the drug is continued, the symptoms tend to return and that if the dose be increased not only may the beneficial results fail to appear, but the symptoms may even be exaggerated.

(117)  
Weller says that the iodine gives good results in exophthalmic goitre though it is not curative; it reduces the pulse in a few days, also the palpitation, the diarrhoea and the vomiting; the weight increases and the amenorrhoea stops, the goitre is decreased in size and becomes harder.

(118)  
Boothby concluded from a study of the disease following ligation, when large doses of iodine were administered continuously for long periods, that after the initial improvement the patient/

patient becomes stabilised. Repeated observations on the effect of iodine given continuously for a year or more have confirmed this, so there is no rational basis for giving it in the hope of curing the disease.

(119)  
Dautrebande and Lemort consider that the opinion that iodine is only of use in pre-operative and post-operative treatment needs revision. They give prolonged treatment in progressive doses, using the basal metabolic rate as their indicator, and claim that in 80 per cent. of their cases a rise in metabolism has been overcome in this way. They believe that exophthalmic goitre is a local affection, determined by general causes, and that iodine lowers the basal metabolic rate and causes disappearance of the symptoms.

(120)  
Caldbrick believes that prolonged treatment is definitely harmful and quotes five cases of his personal observation.

(121)  
Lastly, Frazer states that while he believes there is a definite dosage of iodine which will help every case, he agrees with Macnee that the response to iodine in patients with circulating failure is decidedly poor.

#### Dosage.

Plummer advocates the use of Lugol's solution by *h*gt.i.d. for the 10 days previous to operation/



operation, and during the post-operative reaction, and then  $\eta \overline{x}$  daily for the next eight weeks. Should a recurrence ensue, he gives iodine for three months, and failing complete control does a second operation.

(111)  
Jackson gives  $\eta \overline{x \times x}$  for 3 days, and for two days before operation, after which he continues with a smaller dose.

(114)  
Dunhill thinks that too much iodine is usually given - he finds  $\eta \overline{x}$  once daily quite sufficient. Cole gives  $\eta \overline{v} - \overline{x}$  t.i.d. for the first few weeks, and then  $\eta \overline{v}$  t.i.d. to some (111) patients for as long as six months, and Walton gives Lugol's solution  $\eta \overline{iii}$  t.i.d. in his cases. (119)

Dautrebrande and Lemort use the following solution:

Iodine v 10 gms.  
Pot. iod. 20 gms.  
and aqua to 100 c.c.

They start with  $\eta \overline{x}$  and increase to  $\eta 100-150$  daily over a period of months.

In the writer's experience much good has resulted from the administration of iodine in small doses.

Whereas the use of iodine in the pre-operative treatment of exophthalmic goitre is now universally admitted, the general consensus of opinion/

opinion is that it is contra-indicated, if not dangerous, to give iodine over any length of time, the danger being that of hyperthyroidism.

The writer has administered iodine as potassium iodide starting with gr.  $\frac{1}{11}$  in the day, and soon reducing the dose to gr.  $\frac{1}{2}$  or gr.  $\frac{1}{4}$ . The effect was that, within 48 hours as a rule, the pulse had dropped considerably in rate, and the patient felt much better. By the end of a week the maximal drop in pulse rate had occurred, the exophthalmos had started to recede, and the glassy stare had disappeared from the eye, and the nervous symptoms had vanished. The small dose of potassium iodide gr.  $\frac{1}{4}$  was found to keep up this reduced pulse rate;—its absence was followed by a rise again - and the thyroid became smaller and usually more firm; the weight increased and the basal metabolic rate fell. No signs of increased hyperthyroidism were observed. The greatest response was found in the more toxic cases; in those cases with cardiac failure already present, the effect was the most difficult to judge. The two patients who felt the floor rising and falling in front of them lost this sensation, and stated that they felt better than they had done for years.

The action of potassium iodide is seen in the following graphs.

On/

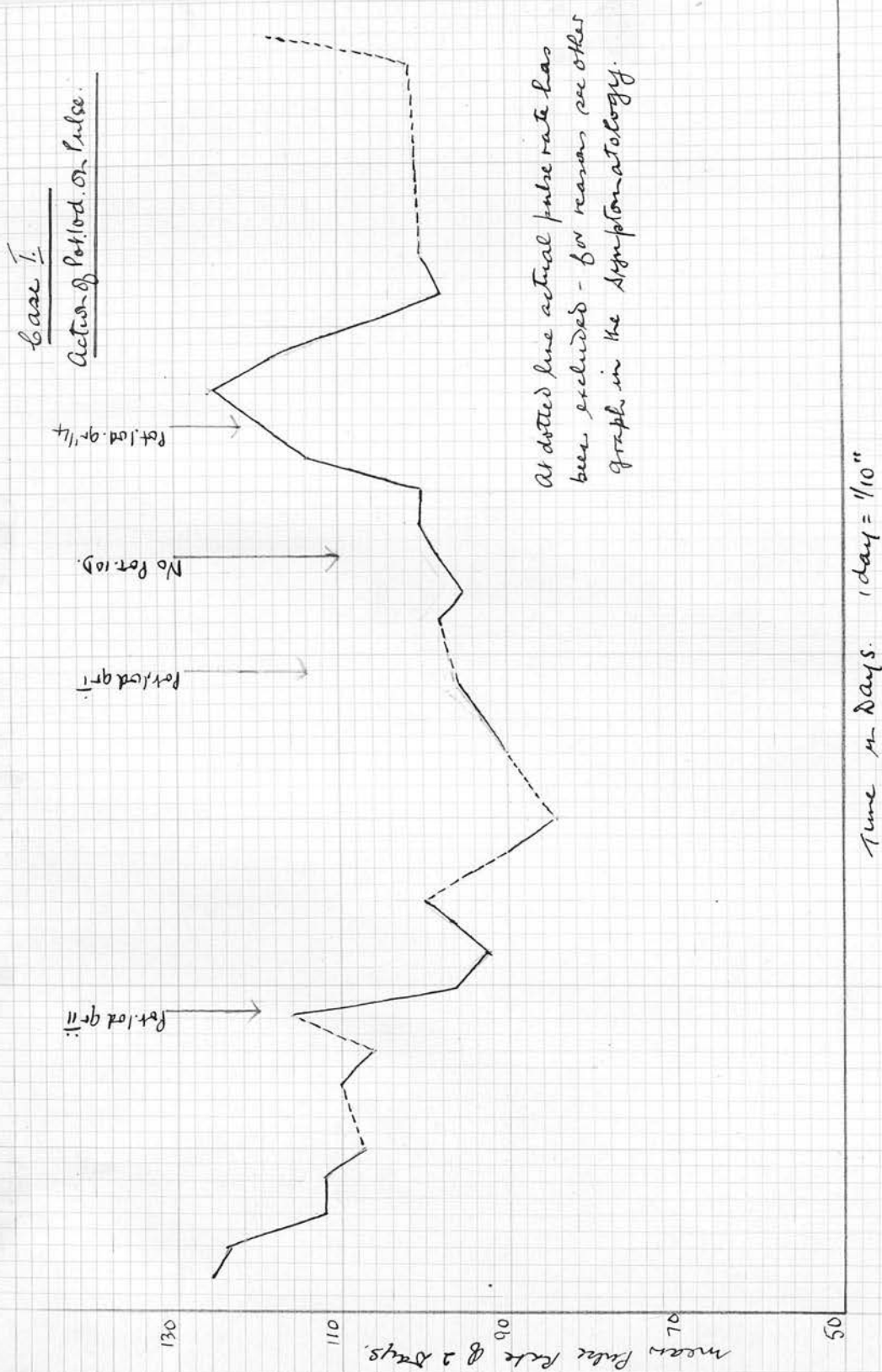
On the pulse rate - Case 1, 2, 3, 4, 5, 11, 24.

On the basal metabolic rate and weight - Case 1. (Graph 8)

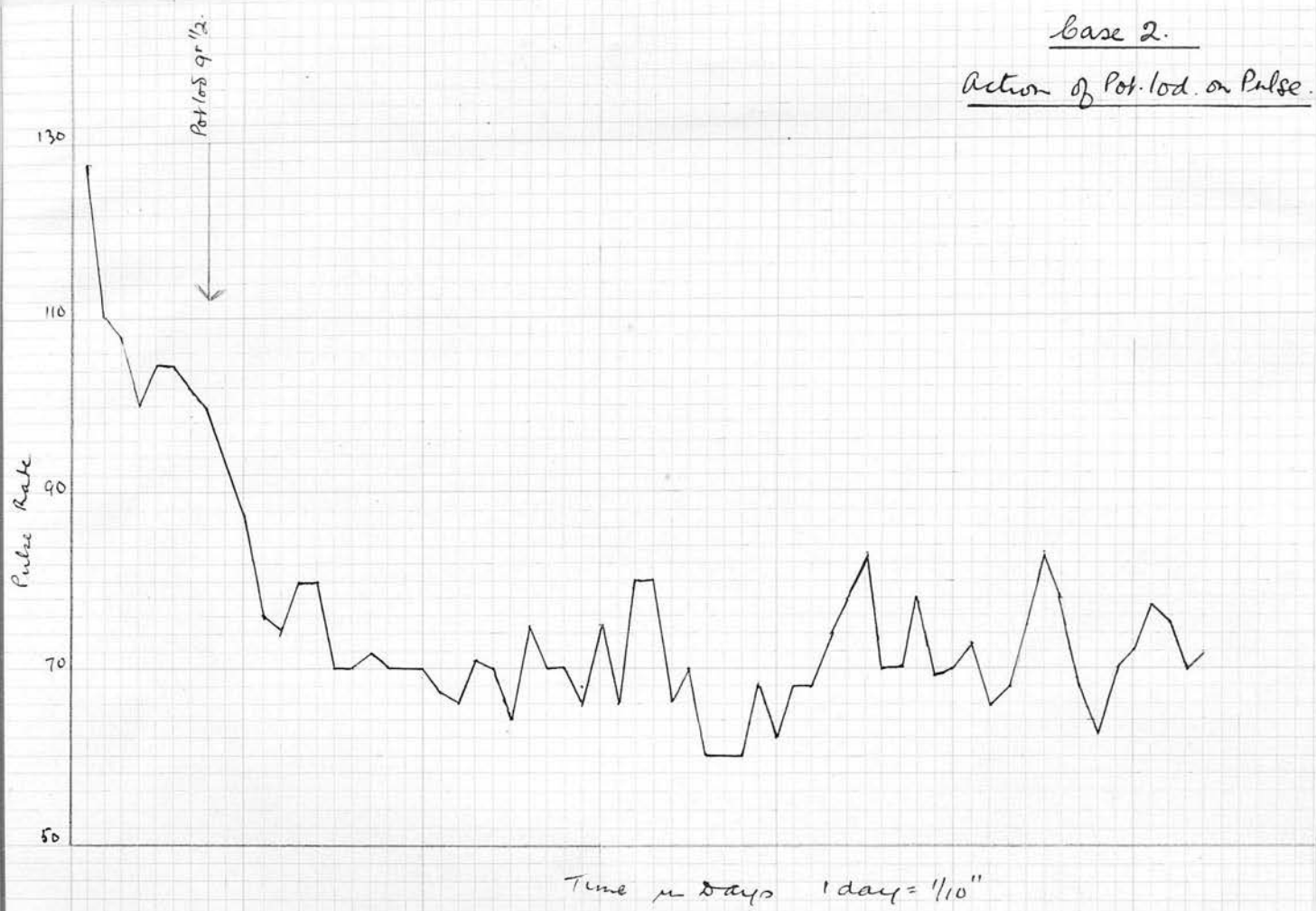
A graph from Case 1 was rendered very difficult by reason of the remarkable response of the pulse to extrinsic influences. The writer was able to define most of these influences; they are defined at the foot of the chart. (Graph 3)

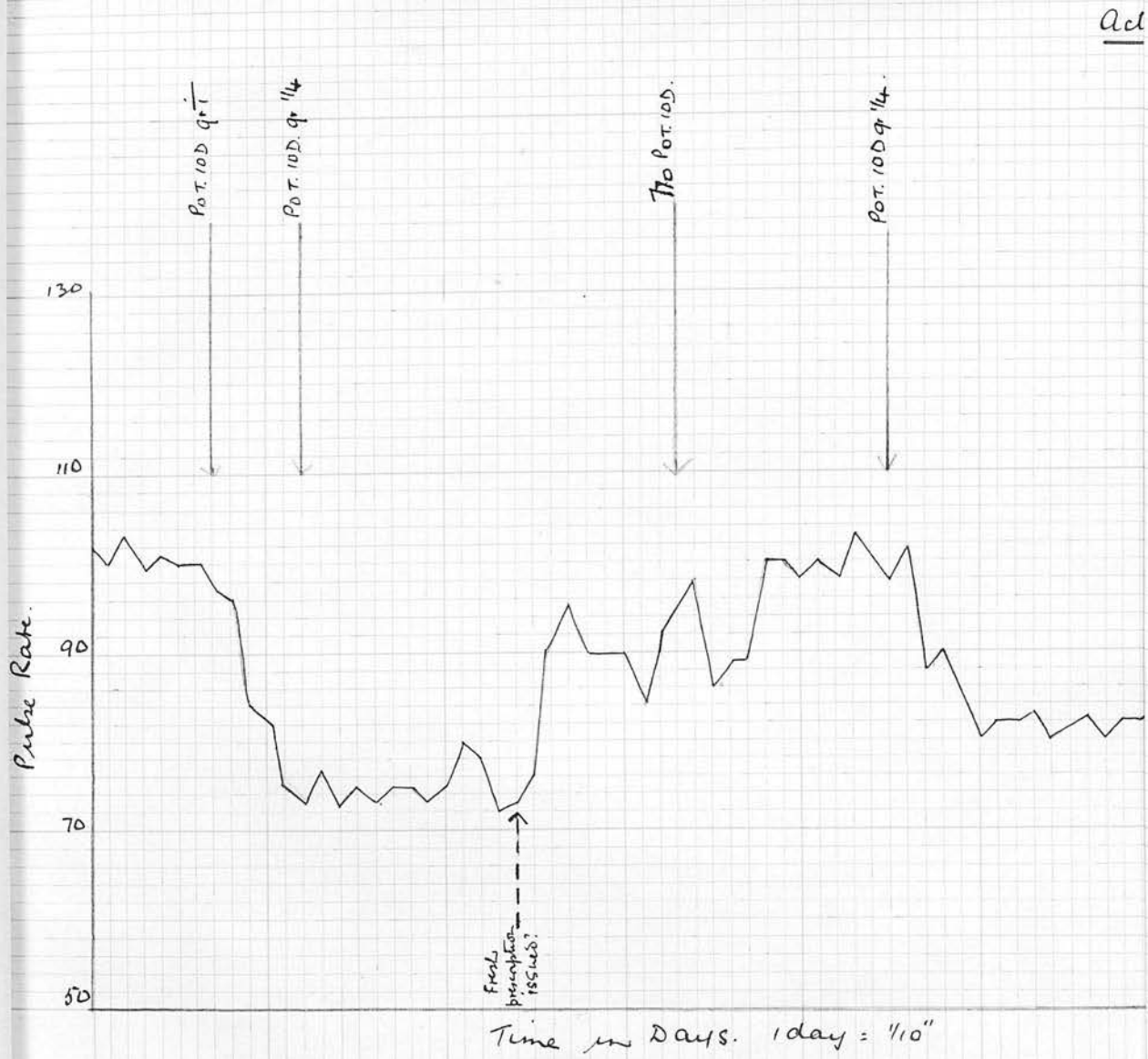
The writer believes that such small doses of potassium iodide can be exhibited over long periods of time with advantage in this condition; that the danger of hyperthyroidism from its administration is exaggerated.

Graphs/

Graph 10.

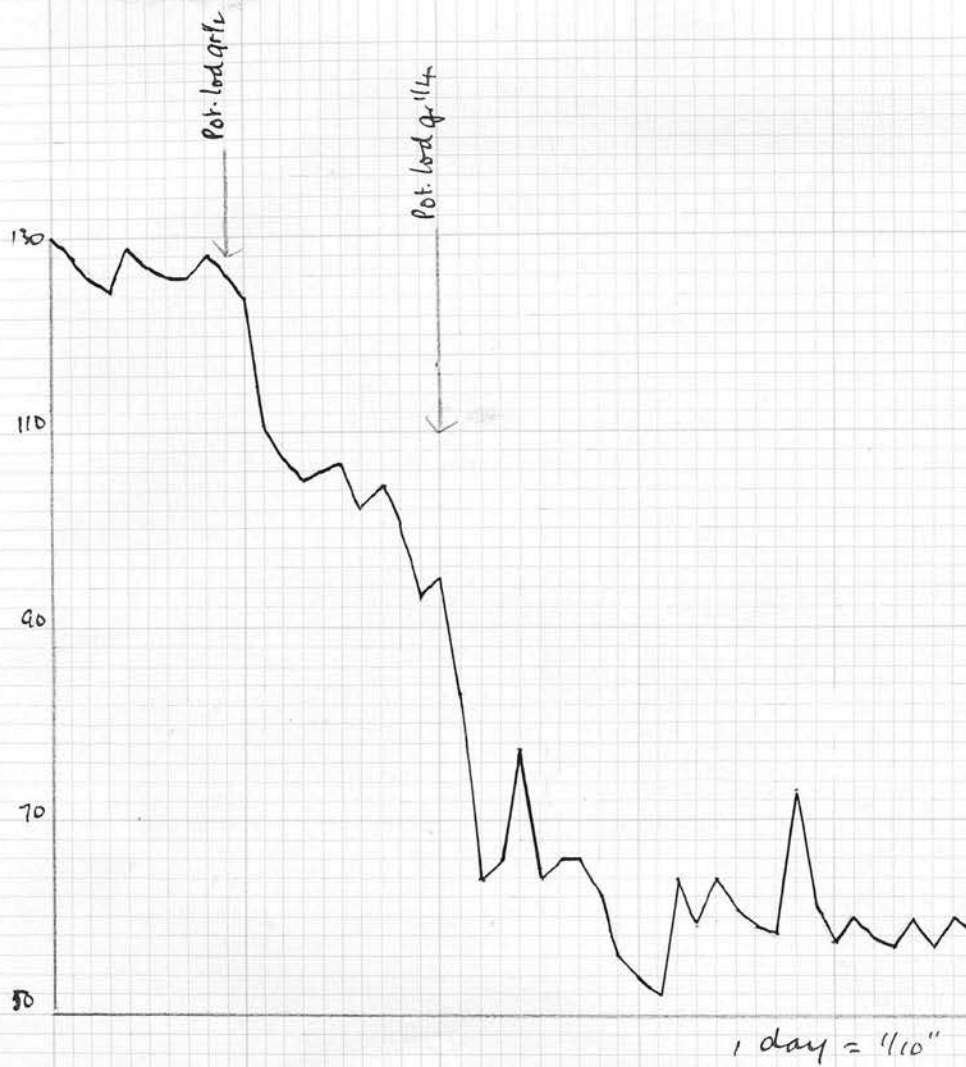


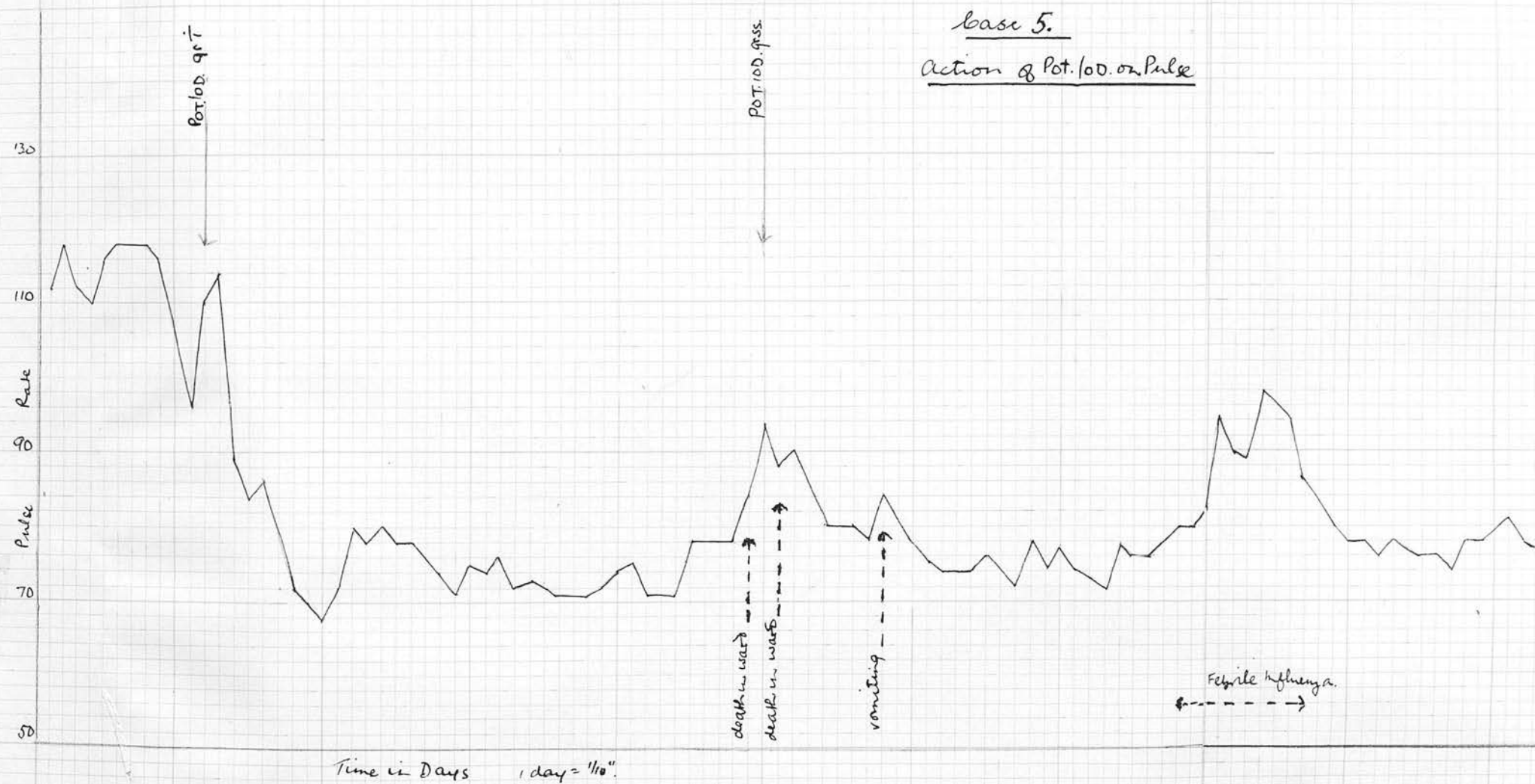
Graph 11.

Graph 12.

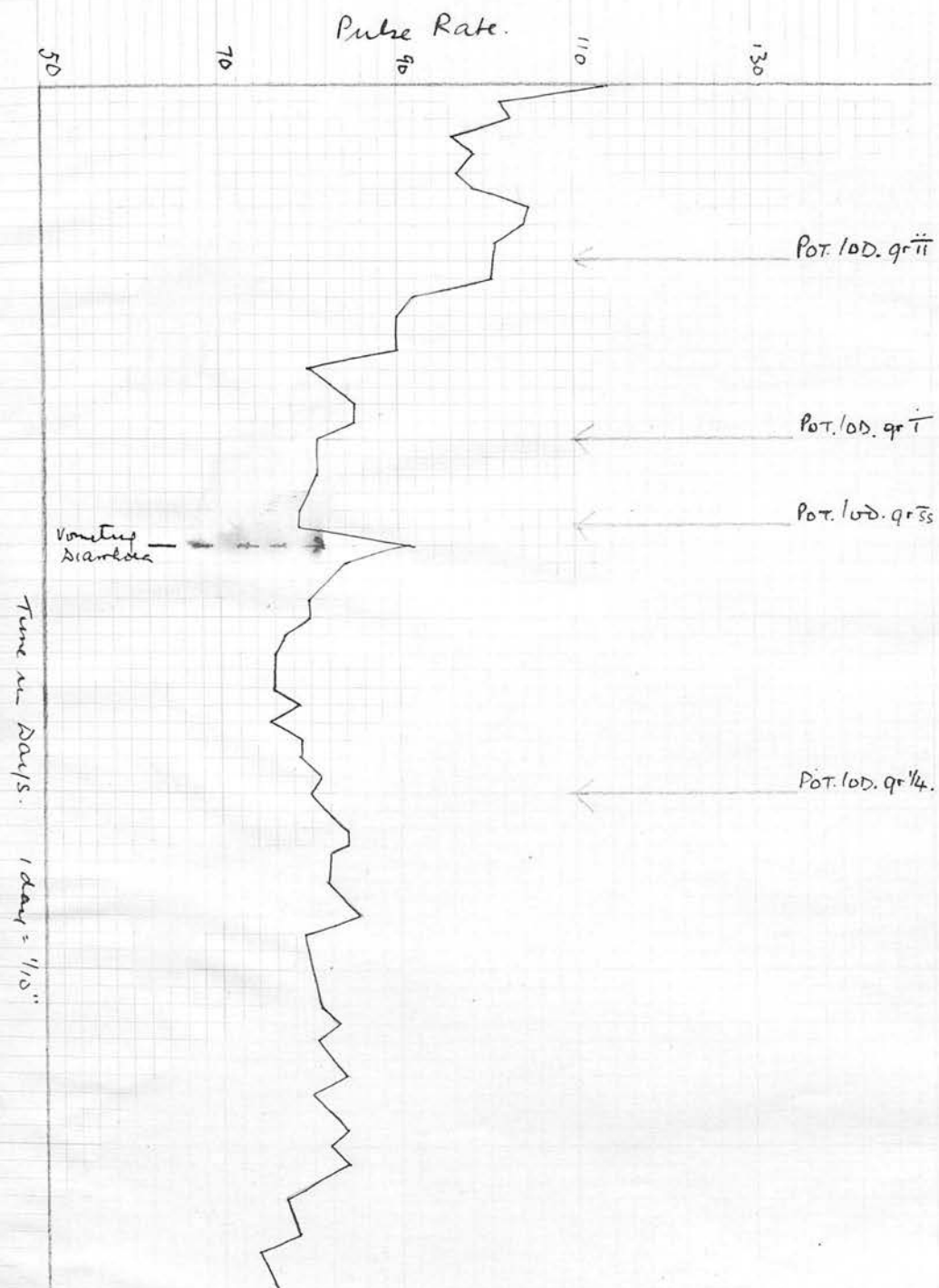
Graph 13.

base 4.  
Action of Pot. lod. on Pulse.



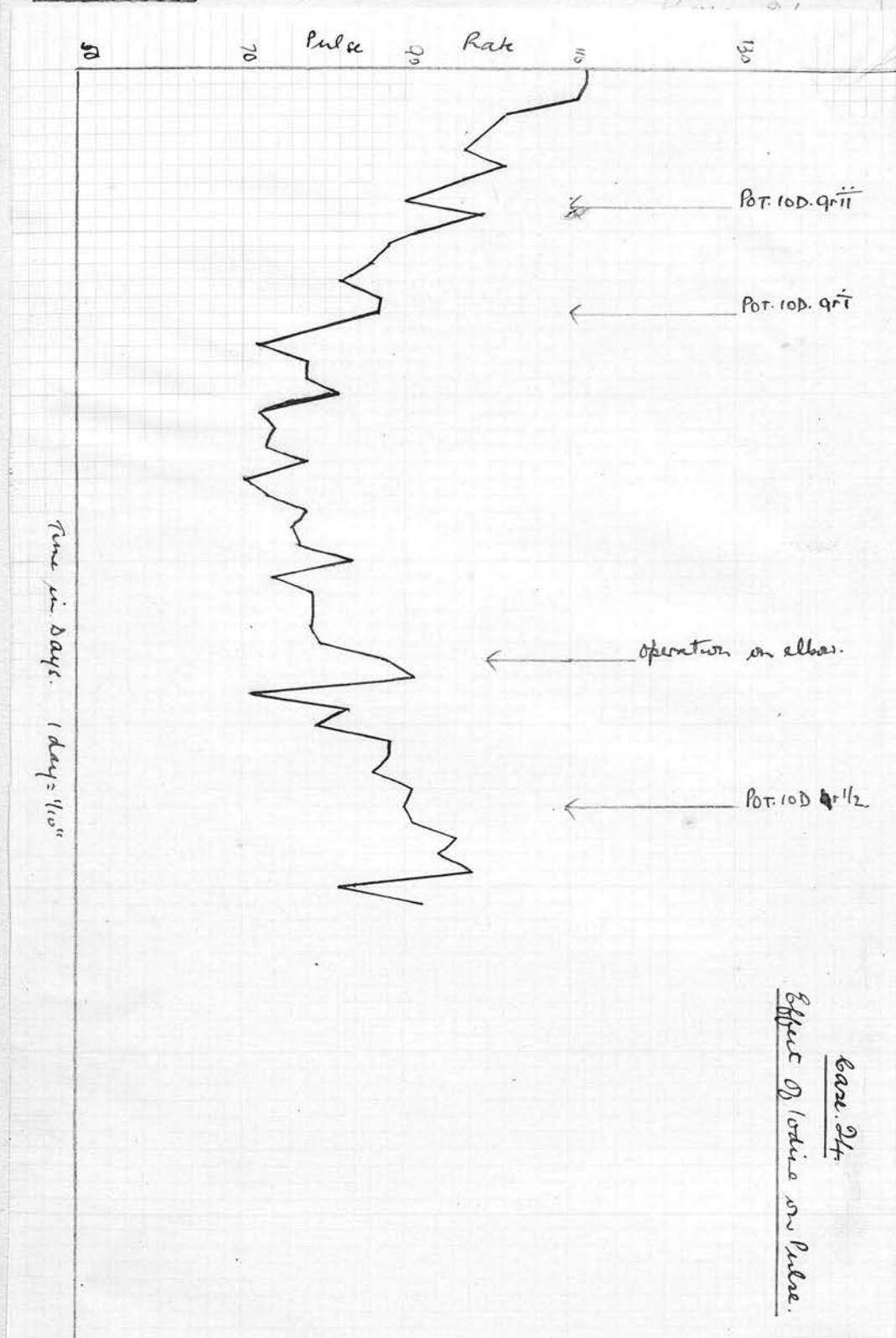
Graph 14.



Graph 15.

Base II.  
Action of POT. LOD. on Pulse.

Graph 16.



Insulin.

Insulin has been tried in this condition on theoretical grounds - whether it is of real value as a therapeutic agent yet remains to be seen. In exophthalmic goitre as in diabetes there is not only a hyperglycaemia but also a glycosuria, although in exophthalmic goitre the amount is always very small.

The rationale would seem to be as follows:- Whereas insulin is antagonistic to the withdrawal of glycogen from the liver, thyroxine favours it, and there is normally a balanced action between the two. In exophthalmic goitre, however, there is an excess of thyroxine, and whereas the amount of pancreatic hormone is actually normal, compared with the amount of thyroxine, it is relatively deficient. Insulin is therefore given in the hope that it may make good this relative deficiency and restore the balance. The administration of insulin should (1) prevent the loss of sugar in the urine, and (2) restrict the excessive combustion of sugar - owing to its antagonistic effect to thyroxine and in so doing it should reduce the basal metabolic rate.

Since the hyperglycaemia and glycosuria are very small in amount, care must be taken in the use of insulin to prevent a hypoglycaemia. Such did occur in Case 2. Patient with an almost constant glycosuria/

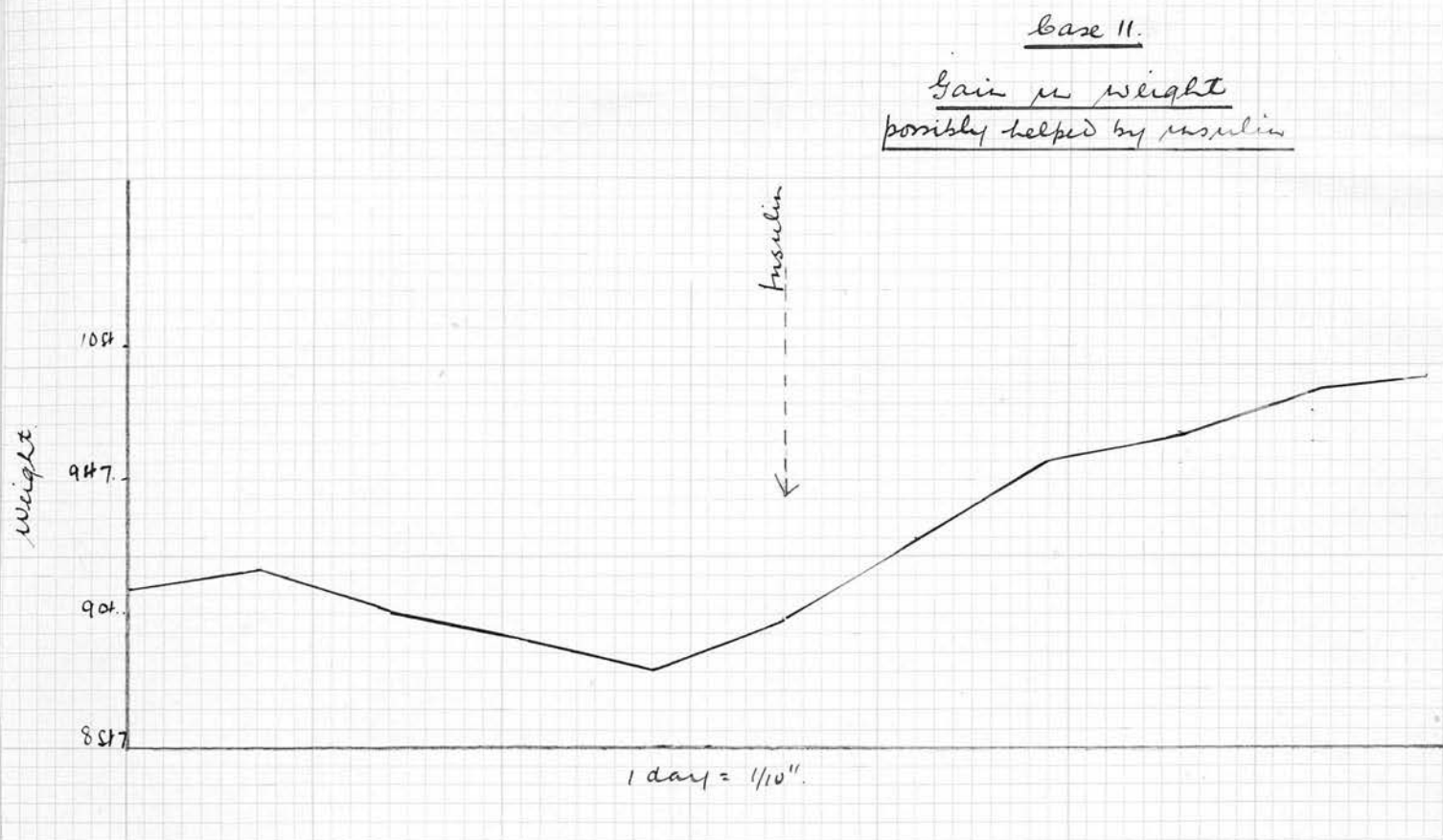
glycosuria was given 5 units of insulin t.i.d. She developed nervousness, sweating, tremors and palpitation, and on administration of sugar lost these symptoms immediately.

One factor in insulin treatment noticed in Edinburgh Royal Infirmary was that the hypodermic injection was accompanied by pain, and much local reaction. It was further observed that the administration of glucose previous to the insulin injection diminished this local reaction. This was observed in Case 1 and more especially in Case 7; in the latter case 45 gms. of glucose abolished the pain, but the dose had later to be increased to 60 gms. to produce this effect.

It is deemed unwise to attribute the remarkable gain in weight in Case 1 to the action of insulin; it would seem possible, however, that the gain in case 11 was at least partly attributable to insulin ~~and~~ since its administration was followed by a gain in weight of 4 lbs. in both of the weeks following its exhibition.

Graph 17/



Graph 17.

Other/

Other drugs believed to be of use in the condition are:-

1. Quinine - usually given as neutral hydrobromide of quinine, gr. V. in capsule t.i.d. for months or even years. Patients with exophthalmic goitre are remarkably tolerant of this drug. Quinine was apparently given in the belief that it decreased the amount of protein metabolism which is excessive in this condition. <sup>(122)</sup> Cushny believes that this is quite unfounded. He states "The metabolism is often said to be reduced by quinine, more especially that of the proteins, while the excretion of carbonic acid and the absorption of oxygen is universally stated to be unchanged. Careful experiments by Hardikar have failed to show any alteration in the protein metabolism either in man or animals under treatment with large doses of quinine. Under the older view quinine was believed to conserve the stores of protein in the body and to have a special value in wasting diseases and fevers from this 'roborant' action."
2. Potassium Bromide, gr. X-XV. t.i.d. is useful for its sedative action as is
3. Belladonna though most patients object to its use/
4. Sodium Phosphate, gr. 15-60 t.i.d. enjoys much popularity/

popularity, especially for the headaches of this condition; its action is probably that of a purgative.

5. Arsenic given in small doses over long periods with intermissions is widely used.

6. Intestinal antiseptics such as sodium benzoate, naphtholene and kaolin are widely exhibited by those who favour the theory of intestinal toxæmia as a causative factor.

Collosol Argentium is found very soothing to the eyes in this condition.

#### Endocrine Therapy.

Extracts of thymus, ovary, pituitary and adrenals have been used without result. Thyroid extract was once given, but it is now universally recognised that it is definitely contra-indicated in this condition.

#### Serological Therapy.

There seems to be no physiological basis for the use of sera in this condition. Many have been tried, but their use is becoming more and more discarded. The idea apparently was that these sera might exercise an antitoxic effect - there seems to be no adequate reason, however, why an antitoxin should be produced.

The/

The two preparations most in vogue were:

(1) Rodagen - a precipitate prepared from the milk of thyroidectomised goate (the fresh milk had also been used).

(2) Antithyroidine (Merck) suggested by Moebius - representing the blood serum of thyroidectomised sheep.

Another preparation, thyroidectin, representing the dried blood of thyroidectomised animals, was also tried.

Burghart even treated patients with serum from patients with myxoedema and claimed good results.

Serum treatment has now been almost wholly abandoned; there is no evidence that the results are any better than those obtained by rest alone.

#### Spondylo Therapy.

(41)

Barr believes in the Albert Abrams' reflex of cardiac contraction in this condition. He states that concussion of the 7th cervical vertebrae causes the heart and arteries to contract, and if the 2nd dorsal spine is now concussed, this reflex is kept up for an hour or two - the latter being the fixation complement. One patient (J. Sharpe) (Case 2) had been induced by her family doctor to go through this performance daily; needless to say, she failed/



failed to benefit by it.

### Psycho Therapy.

Psycho therapy is advised by Stoddart who claims to reduce the pulse to normal in 4-6 months, and by Beebe<sup>(123)</sup>. It is pointed out that injury of some kind to the nervous system is, even if not a primary factor, at least a very important one in the etiology of the condition; that symptoms referable to it predominate in the clinical picture, and that psycho therapy plays an important role in relieving these symptoms.

The writer has no experience of psycho therapy.

### X-rays.

X-rays are believed to have a definite therapeutic effect in this condition. The supporters of this treatment state that it is followed by a rapid fall in the pulse rate, lessened tremor and nervous symptoms, the gland decreases in size and becomes less vascular, and the body weight increases.

The advantages of X-ray treatment are that there are no immediate fatalities, no operation scar is seen, no interference with work occurs, the treatment is painless and, should it fail, operation can still be performed. The disadvantages are that treatment is tedious, lasting months, that/

that telangiectasis and scarring of the skin may occur, that the dose is a guess, that operation after X-ray treatment is rendered more difficult, and lastly, that relapses are common.

(124)  
Hutchison states that the general opinion is that X-rays are disappointing; the general symptoms are not affected, and the reduction in size of the gland is not always permanent. (125)  
McGregor believes that X-rays and radium improve bad cases, and reduce the basal metabolic rate, but will not hold them, and Berkman (126) confirms this view.

(127)  
Storey quotes the following figures from X-ray treatment: of 200 cases 78 were cured, one developed slight myxoedema, 60 were better and able to work and 10 died. (128)  
C.A. Joll states that X-ray treatment is not very successful and mentions that 32 out of 50 consecutive cases coming to him for operation had had previous X-ray treatment.

(129)  
C. Thurstan Holland and J. Morley believe that X-ray is one of the chief avenues of approach to the cure of exophthalmic goitre. (130)  
J. Douglas Webster states that the radiological view may be put thus: "Of those patients who are not cured by medical measures only, a small percentage cannot be relieved by radiation while a large percentage are cured."

(131)  
Lastly Murray quotes the following results/

results supplied him by D. Woodburn Morrison on X-ray treatment of 100 consecutive cases:-  
 completely recovered 27 per cent; good functional result 49 per cent; slight improvement 19 per cent.

In this series four cases are taken as illustrative of X-ray treatment:

(1) Case 9. After 6 months X-ray treatment. When seen was on the way to complete recovery, slight exophthalmos being the sole surviving sign. She was a mild case, however, and it is possible that she would have recovered with medical measures only.

(2) Case 3. Previous X-ray treatment for 10 months. Thyroid not now enlarged, firm, and not vascular, but general symptoms only slightly improved by treatment. Tachycardia (P. 110 per minute) and palpitation, nervousness, slight tremor, and vasomotor phenomena still present.

(3) Case 8. A bad case, fully developed picture of the disease with cardio-vascular damage already evident; had radium with temporary improvement for two months, after this both radium and X-rays failed to show any effect, except for more than usual firmness of the thyroid.

(4) Case 21. 14 months X-ray treatment, later followed by subtotal thyroidectomy. Thyroid reduced in size and very hard, some atrophy and fibrosis of the skin present, general symptoms still marked.

It would therefore seem that X-rays is by no means a sure method of treatment. It does admittedly reduce the size and vascularity of the thyroid gland - it may cause a temporary improvement, but it seems to have no effect on the general symptoms of the condition.

### Radium.

Radium possesses two advantages over X-rays - the period of treatment is shorter and the intervals between applications is longer, and a definite dosage is possible. <sup>(132)</sup> H. French believes that radium is less certain in its action even than X-rays, while <sup>(133)</sup> Aikins records cure of six cases where all else had failed. It has one disadvantage over X-rays - the first application in very severe or acute cases may cause an increase in the hyperthyroidism, which may even result in death. <sup>(134)</sup> Burrows from a series of 180 cases treated in the Manchester and District Radium institute claims a cure in 31.6 per cent. of cases.

While radium was applied in several cases in this series, only one case had been so treated for a sufficiently long time to base an opinion on it. Like X-rays it seemed to have a local effect on the thyroid, causing diminished vascularity and reduction in the size of the gland - it left the general/



general symptoms untouched.

Case 4 - treated by radium for 2 years. Thyroid small and firm and not vascular. Several symptoms pronounced. Tremor marked, tachycardia and palpitation (130 per minute). Exophthalmus stare, and vasomotor symptoms all present.

On this somewhat meagre evidence radium would not seem very efficacious.

#### Electricity.

Mild faradic current has been advised in this condition, where X-rays are unavailable. Electrodes are placed on the front and back of the neck and a current just strong enough to produce tingling of the skin is passed through the gland for 1-2 hours daily. Treatment is prolonged, extending over 12 months, and results are claimed. It is dubious, however, if electro-therapeutics have any effect whatever in this disease.

#### Injections.

Injections into the gland have been advocated as a method of diminishing thyroid output by fibrosis without the same risk as operation. Boiling water was used by Mayo, and other authors have used iodine, iodoform, carbolic acid, glycerin.

Sheehan/

(135)  
 Sheehan recommends injections of 5 drops of equal parts of carbolic acid, iodine and glycerine, at five day intervals and states that five injections usually suffice.

This method is certainly not devoid of danger, and its popularity has most certainly waned.

### Surgical Treatment.

Whether surgery is ever justifiable in exophthalmic goitre is the chief bone of contention in the treatment of the disease.

The exponents of surgery point out that though the thyroid may not be the primary seat of Graves' disease, it is the circulating poison elaborated in the thyroid gland which acts as the toxin on viscera, and removal of part of the gland is the most direct method of reducing the output.

(131)  
 Murray summarises the advantages of operation in primary Graves' disease, as

- (1) the saving of time from the economic point of view, owing to the prompt reduction of thyrotoxicosis and immediate relief of symptoms.
- (2) The complete recovery in some cases and the partial improvement in others.
- (3) The diminution of the risk of chronic myocarditis and digestive changes in other organs.

He enumerates the disadvantages as -

(1)/

- (1) the risk to life.
- (2) the uncertainty of the ultimate result of the operation owing to the difficulty in determining the right amount of thyroid to be removed in each case.
- (3) the tendency for the disease to recur in a year or two and so necessitate further medical or surgical treatment.

On these points Dunhill would seem to be in entire agreement. He holds that if a patient is grievously ill and cannot by any medical means be restored to an industrial plane, then surgery must have its chance. In his opinion when a patient, and more especially one who has to earn his own living, has had the disease for six months the question of operation is certainly arguable; but where auricular fibrillation has been established and congestive cardiac failure has occurred, the question has ceased to be arguable. Neither rest nor medical nor X-ray treatment will restore the patient to health, whereas he believes that surgery will remove both the congestive cardiac failure and the auricular fibrillation.

The opponents of surgical treatment see the disease from a totally different aspect. They point out that the thyroid plays an incidental part in the syndrome, and therefore to attack it is etiologically/

etiologically, physiologically, pathologically and clinically fallacious; for exophthalmic goitre does not spring up in a night like Jonah's gourd, nor does it wither away even under the surgeon's knife. They show that the remaining gland portion usually hypertrophies and that the immediate beneficial results are not permanent, and ask the surgeon for what length of time does he follow up his cases after operation.

They agree that the surgeons have a very definite mortality, variously given from 1-5 per cent., and ask if this is the operation mortality alone, or does it also include the mortality of preliminary ligation and that occurring some weeks after operation, and do the figures not include both exophthalmic goitre and toxic adenoma.

They mention such first operative sequelae as vocal paralysis, tetany, ~~anyxoedema~~, acute and often fatal ~~exacerbation~~ and acute psychosis, and they conclude by stating that surgical text-books do not deal with the disease as a disease, with cures and after results, but only as an opportunity for beautiful exposition of the *modus operandi* of surgical attack on the gland.

The literature of exophthalmic goitre abounds with such controversial sentiments, of which a few may be pardonably quoted.

"There are few subjects on which the surgeon can be less didactic as to the merits of  
of/



of surgical versus medical treatment than on that  
 of hyperthyroidism."(Deaver<sup>(136)</sup> ).

"Reviewing the whole subject of the  
 operative treatment of exophthalmic goitre it seems  
 to me that it may be reasonable doubted whether  
 surgical treatment is not on the whole worse than  
 useless."(Frazier<sup>(137)</sup> ).

"It is.... impossible at present to give  
 surgical treatment the preference over medical  
 means" (Haberer<sup>(138)</sup> ).

"The practice of operative interference with  
 the thyroid gland, in all cases of Graves' disease  
 at sight, is a common custom at present, and  
 without applying all the resources of our art in the  
 detection of its cause, is one that cannot be too  
 strongly deprec~~ated~~ated. I am convinced that the  
 number of cases in which thyroidectomy is performed  
 will become smaller and smaller, its practice will  
 ultimately be abolished." (McCarrison<sup>(1)</sup> ).  
 (139)

Leonard Williams believes that there is  
 no more justification for ablation of one lobe of  
 the thyroid in Graves' disease, than there would  
 be for the removal of one kidney in diabetes.

(140)  
 Lastly Sir J. Berry says "In the very  
 great majority of cases of true Graves' disease  
 I have declined to operate as I have not considered  
 that/

that the benefit to be obtained justified the risks."

The case for the surgeon could also be quoted ad nauseam but it is well summarised by Dunhill as follows:

- (1) The exophthalmos will improve and may be cured.
- (2) Rapid improvement in the cardio-vascular system will take place, and the auricular fibrillation may entirely disappear.
- (3) Glycosuria will disappear, or failing that, be easily controlled.
- (4) Weight will rise and loss of anorexia occur.
- (5) Mental disorder, if present, may be cured.

He points out that if four-fifths of a toxic secretion, which has flooded the body for years, is expurgated, the relief on the organs is enormous and may be dramatic. While the condition of the patient is rarely quite a normal one, it is much nearer normal than it would have been without operation.

A.J. Walton gives the following figures as the result of operation - an immediate mortality of 5 per cent, a late mortality of 2 per cent, the certainty of complete cure in about 55 per cent. and sufficient relief for the patient to earn his own living in 81 per cent. The most satisfactory results published in England are probably those of/

(141).  
 of Berry . Of 78 cases, 53 (70 per cent.)  
 were almost cured, 18 were better, 4 showed no  
 change and 3 died.

A discussion of the various operations is  
 hardly within the sphere of the physician. It is  
 sufficient to state that ligation of thyroid arteries,  
 partial thyroidectomy, and subtotal thyroidectomy  
 are the routine operations, the last named being  
 the usual one. Within recent years Haberer<sup>(44)</sup>  
 believes in the removal of as much of the thymus  
 as is possible at the same time as the subtotal  
 thyroidectomy, while Caldbick<sup>(120)</sup> even advises  
 that the whole thyroid be excised, and the  
 deficiency made good by oral administration of  
 thyroid extract.

What, then, is the physician's duty both  
 to his patient and also to his surgical colleague?  
 There is complete unanimity of opinion that treat-  
 ment in the first six months is medical. After  
 six months of treatment with no response, and  
 still more so at the first sign of commencing  
 cardiac failure or auricular fibrillation, it  
 would seem the physician's duty to ask the  
 patient to consider consultation with a surgical  
 colleague re operation. At the same time it is  
 only fair to the patient to point out that the  
 operation/

operation is attended by a very definite risk to life, and that its success varies, although the result might be beyond his wildest expectation.

The writer's experience of surgical treatment of exophthalmic goitre has not been a happy one, though the number of cases has been very small. In Edinburgh one case (Case 15) had to be certified insane - she had undergone a partial thyroidectomy in Canada some years before. This would bring out Braun's opinion <sup>(73)</sup> of the predilection of the toxins of exophthalmic goitre for the nervous system after operation. In Sunderland two post-operative cases were in the medical wards: (1) <sup>(Case 22)</sup> a Welsh, aet. 41 - greater part of thyroid removed five years before, complained of nervousness, dizziness and exophthalmos, and (2) Case 21, after both X-rays and subtotal thyroidectomy still had palpitation and tachycardia, tremors, and exophthalmos. She had much improved by her first operation, but hypertrophy of the other lobe had occurred, probably subtotal resection of the remnant would have benefited her exceedingly.

The last three cases seen operated on all died; one in post-operative crisis, the other two suddenly from cardiac failure. It seems to the writer that the operative death rate of exophthalmic goitre in Great Britain and Ireland, if investigated, would certainly show a much higher mortality than 2-5 per cent.



VII. Summary and Conclusions.

VII. Summary and Conclusions.

- (1) Exophthalmic goitre is a disease which is becoming more common.
- (2) A remarkable rise in the death rate from this condition has occurred in the last few years. This is probably an aftermath of the war.
- (3) The maximum death incidence is 45-55.
- (4) The sex ratio of Great Britain is probably more than 10 females to 1 male. There is a constant death ratio of about 10 to 1 for all ages found over a long series of years; and male cases have a worse prognosis than female cases.
- (5) The cause of exophthalmic goitre is unknown. A combination of psychic and toxic factors occupies a prominent aetiological position. Recent evidence favours the theory of dysthyroidism; the possibility of a diathesis has been brought forward.
- (6) The presence of a loud prolonged systolic murmur over the superior thyroid vessels at the upper poles of the thyroid gland is of diagnostic importance.
- (7) /

- (7) The blood pressure - the systolic blood pressure is increased, the diastolic lowered; the pulse pressure is increased.
- (8) Glycosuria is common in this condition.
- (9) Amenorrhoea would appear more common than menorrhagia.
- (10) The nervous picture is not one of pure anxiety and apprehension. The patient is often very self-confident, her outlook optimistic, her speech incisive, her manner vivacious.
- (11) Mania, melancholia and delusional insanity may be the end result of the condition. The central nervous system is the chief seat of post-operative changes.
- (12) Less widely known symptoms are good appetite when ill, changes in the nails, and an increased tolerance for cold accompanied by a decreased tolerance for heat.
- (13) Rest is the sheet anchor of treatment.
- (14) The administration of iodine produces definite improvement within 48 hours, and marked improvement within seven days. There is a fall in the pulse rate, nervousness is diminished, regression/

(14)  
contd.

regression of the exophthalmos and loss of the stare occur, the thyroid becomes smaller and usually firmer, the basal metabolic rate falls, and the patient increases in weight.

Contrary to the general opinion the writer believes that the role of iodine in this condition is not merely for pre-operative treatment. In doses of potassium iodide gr.  $\frac{1}{4}$  daily, it can be used for months with advantage, and no signs of increased hyperthyroidism ensue.

(15) It is questionable if the exophthalmos ever totally disappears.

(16) The use of insulin in this condition is still to be proved.

(17) X-rays and radium are disappointing; they decrease the size of the gland without exercising more than a slight effect on the general symptoms.

(18) Operative interference is still associated with such a definite mortality that it should not be lightly undertaken.



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## Appendix.

### Synopsis of Twenty-Five Cases.

These cases have been worked at clinically under the scheme formulated by Dr John Eason, my former chief in Edinburgh Royal Infirmary. I am indebted to him for permission to make use of certain of the cases seen during my period as House Physician; fourteen of them are included in this appendix.

Case.	Age.	Sex	married single.	Goitre.	Exophthalmos.	Stare.	Tachycardia.	Palpitation.	Tremor.	Loss of Weight.	Dilated pupils.	Von Graefe.	Dalrymple.	Moebius.	Stellwag.	Joffroy.	Cardiac damage.	Systolic B.P.	Diastolic B.P.	Headache.	Bad Sleep.	Good appetite.	Constipation.	Diarrhoea.	Thirst.	Glycosuria.	Amenorrhoea.	Menorrhagia.	Erythema.	Pigmentation of eyelids.	Emotional disturbances.	Sepsis.
1.	16	F	s	+	+	++	+	+	++	+	+	-	+	-	+	-	+	150	68	-	-	++	-	-	++	+	+	-	-	-	-	-
2.	30	F	s	+	+	++	+	+	++	+	+	+	+	-	+	+	-	150	70	+	+	+	+	-	++	++	-	-	+	+	+	-
3.	27	f	s	+	++	++	+	+	-	+	-	+	+	+	+	+	-	140	90	-	-	+	+	-	+	+	+	-	-	+	-	-
4.	24	F	s	+	++	-	++	+	++	+	-	+	+	+	+	+	-	155	70	-	+	+	+	-	++	++	+	-	+	+	+	-
5.	55	F	m	+	+	-	+	+	++	+	-	+	+	+	+	+	-	170	98	+	+	+	+	-	+	+	-	-	-	-	-	+
6.	19	F	s	+	+	++	+	+	+	+	-	+	+	+	+	-	-	150	108	-	+	+	-	-	-	-	+	-	-	-	+	-
7.	23	F	s	+	+	+	+	+	+	+	-	+	+	+	+	+	-	140	70	-	+	-	-	-	-	-	-	-	-	+	+	+
8.	39	F	s	+	+	+	+	+	+	+	-	+	+	+	+	+	+	162	80	+	+	+	-	++	++	+	+	-	+	+	+	+
9.	45	F	m	+	+	-	+	+	-	+	-	-	+	-	-	+	-	136	70	+	+	+	+	+	+	-	-	-	-	-	-	-
10.	50	F	m	+	+	+	+	+	++	+	-	-	+	+	-	+	-	138	60	-	+	-	-	-	-	-	-	-	-	+	+	-
11.	47	F	s	+	+	+	+	+	-	+	-	+	-	+	+	+	+	135	74	-	+	+	+	+	+	-	-	-	-	+	-	+
12.	30	F	m	+	+	+	+	+	+	+	-	+	-	-	+	+	+	140	72	+	+	-	-	-	-	-	+	-	-	-	-	+
13.	28	F	s	+	-	-	+	+	+	+	-	-	-	-	-	-	-	175	80	-	+	-	-	-	-	-	-	-	+	-	-	-
14.	37	F	s	+	+	+	+	+	+	+	-	+	+	-	-	-	-	120	76	-	+	+	+	-	-	-	-	-	+	-	-	+
15.	49	F	s	+	+	++	+	+	+	+	-	+	+	+	+	+	-	160	68	-	-	-	-	-	-	-	-	-	-	-	-	-
16.	33	F	s	-	++	++	+	+	+	-	-	+	+	+	+	+	-	160	68	-	-	-	+	-	+	-	-	+	+	-	+	+
17.	22	F	s	+	+	++	+	+	+	+	-	+	+	-	-	+	+	140	65	-	+	+	+	-	-	-	-	-	+	-	+	-
18.	22	F	m	+	+	+	+	+	+	-	+	+	+	-	+	-	-	154	80	-	-	+	-	-	-	-	-	-	-	-	-	-
19.	39	F	s	+	++	-	-	-	-	++	-	++	+	-	+	-	+	120	60	-	-	-	+	+	+	-	+	-	-	+	+	-
20.	55	M	m	+	+	+	+	+	+	-	-	+	+	+	+	-	-	180	90	++	-	-	-	-	-	-	-	-	-	+	-	+
21.	33	F	m	+	+	+	+	+	+	+	-	+	+	+	+	+	-	150	82	-	-	-	+	-	-	+	+	-	-	+	+	-
22.	41	M	?	+	-	-	-	-	+	+	-	-	-	+	-	+	-	160	94	+	-	-	-	-	-	-	-	-	+	+	+	-
23.	43	M	m	+	+	+	+	+	+	-	-	+	+	+	+	-	+	142	80	-	+	+	-	-	+	-	-	-	-	+	-	+
24.	36	M	m	+	+	++	+	+	+	+	+	+	+	-	+	-	-	130	70	-	-	+	-	+	+	+	-	-	-	+	+	-
25.	41	M	s	+	+	±	+	+	-	+	-	+	+	+	-	+	+	122	60	-	-	+	+	-	+	+	-	-	-	+	+	-